VOLUME 39 NUMBER 5

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OF

DISEASES OF CHILDREN

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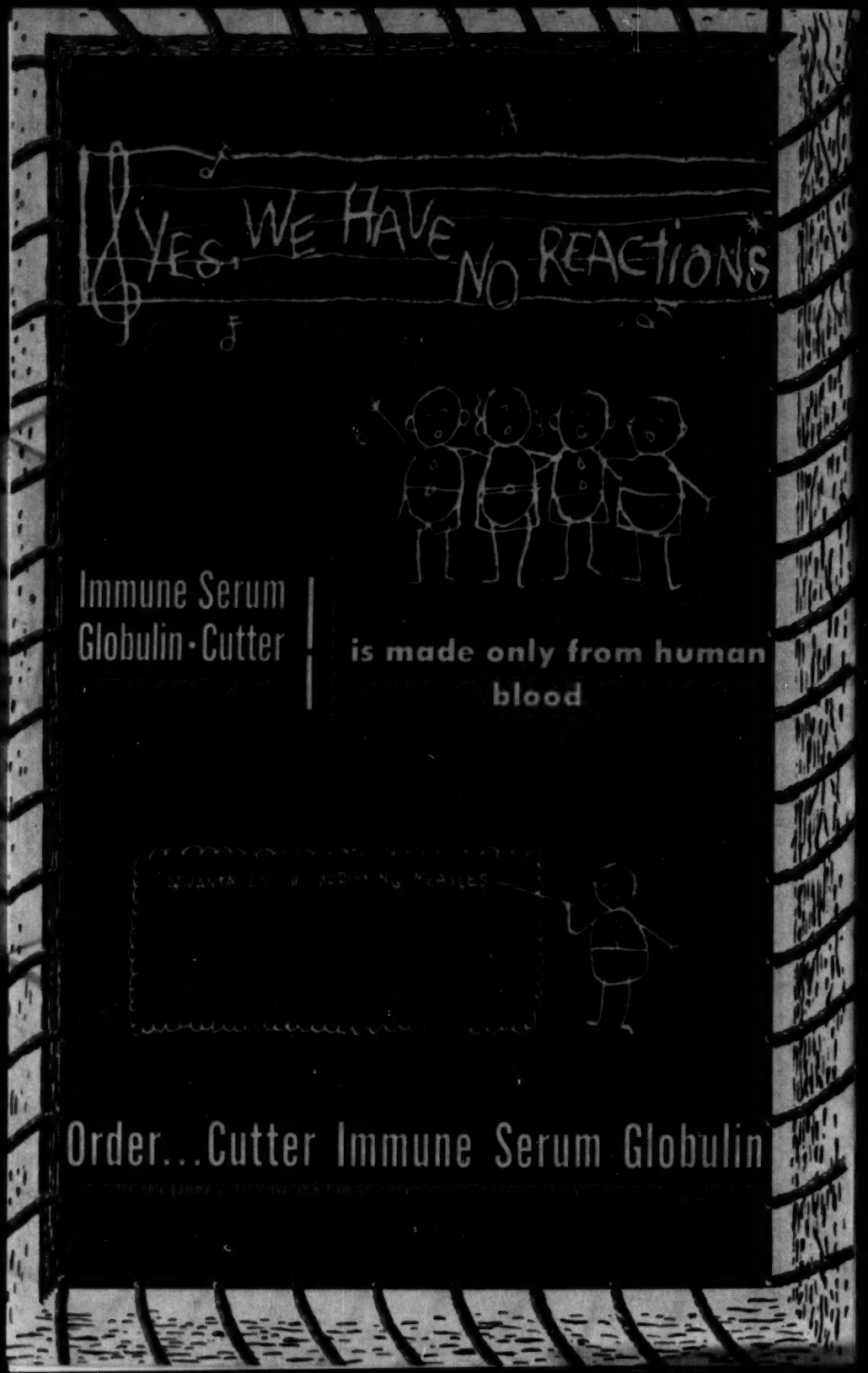
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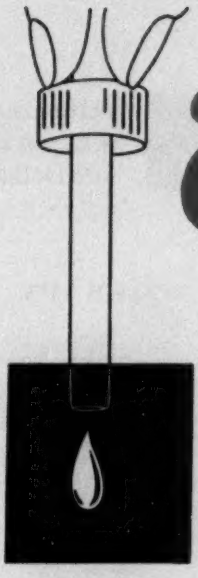

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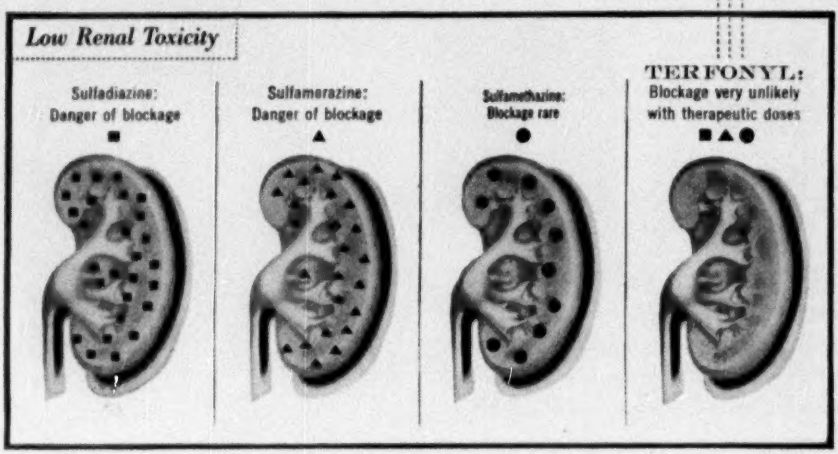

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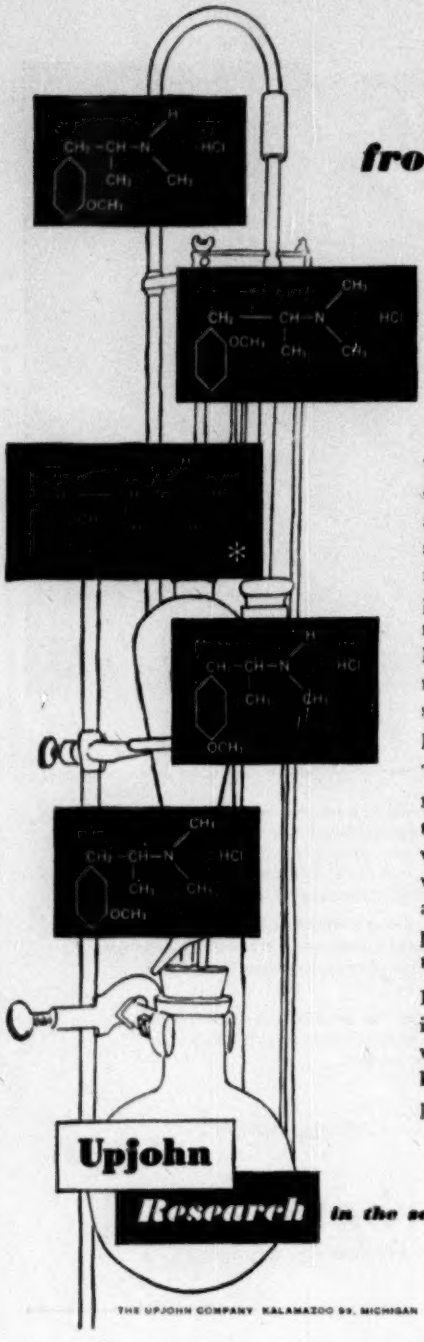

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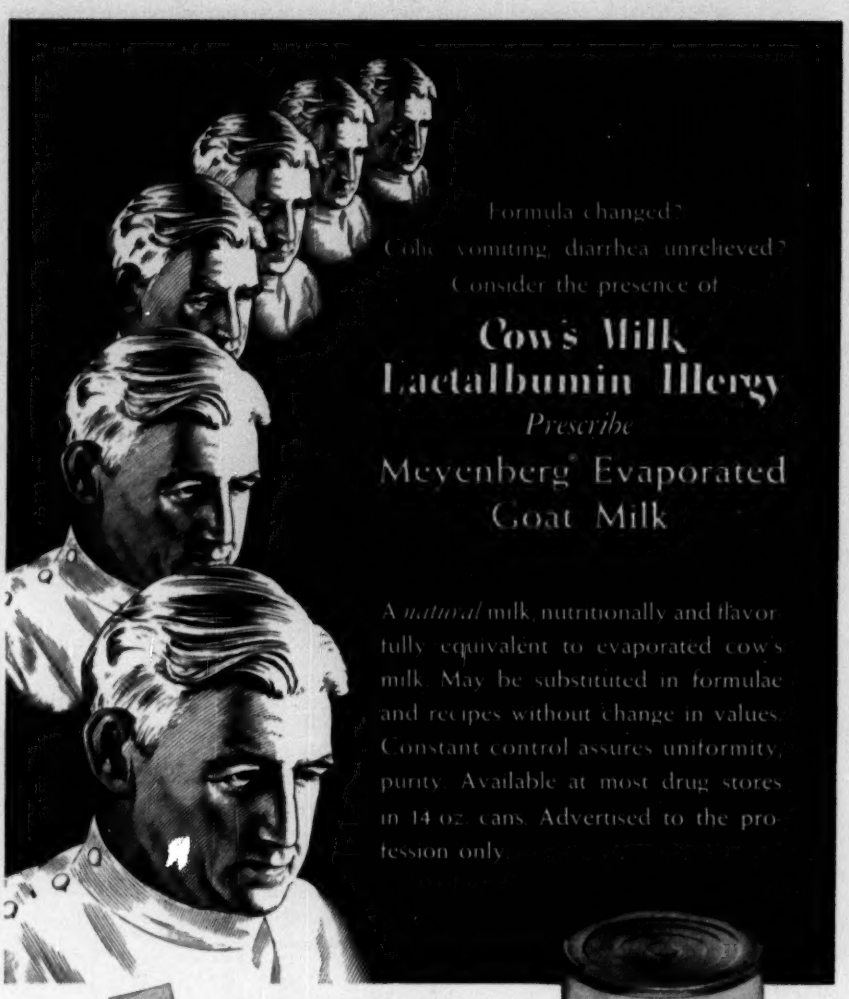
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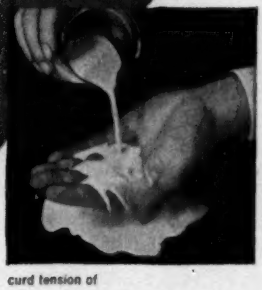

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American Journal of Diseases of Children

VOLUME 79 MAY 1950 NUMBER 5

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CLINICAL OBSERVATIONS ON A NEW SULFONAMIDE (GANTRISIN®)

JOHN A. BIGLER, M.D.
CHICAGO
AND
ORVILLE THOMAS, M.D.
SHREVEPORT, LA.

GANTRISIN,* 3,4-dimethyl-5-sulfanilamido-isoxazole, formerly known as NU-445, is a new sulfonamide which has as its advantages a high degree of solubility and low toxicity. Because of its solubility, there is no crystallization in the urine except with doses that are much higher than would be used therapeutically.

Bryer and his associates [1] reported that the acute toxicity of gantrisin* is low in white mice. They found the drug comparable to sulfadiazine in its ability to protect mice against beta hemolytic streptococcus and pneumococcus infections. It is not as effective as sulfadiazine in experimental infections in mice produced by Klebsiella pneumoniae. Neither compound was protective against experimental infection produced by Hemophilus influenzae, type B. Sarnoff [2] reported neither crystalluria nor signs of renal irritation in 36 patients treated with gantrisin.* He observed that the amount of the drug entering into the spinal fluid of the normal person is low, but in the presence of meningeal inflammation it was greatly increased in the 1 patient studied. In 1 patient to whom 18 Gm. was administered over a period of fourteen hours there were no untoward reactions. This same patient, while being given oral therapy, also received 12 Gm. intravenously within ten minutes. He then exhibited pallor and sweating for a few hours; crystalluria and hematuria were noted for three days, and there was a transient rise in the blood urea nitrogen to 50 mg. per hundred cubic centimeters.

This drug was supplied to us by Hoffmann-LaRoche, Inc., Nutley 10, N. J.

From the Children's Memorial Hospital and the Otho S. A. Sprague Memorial Institute Laboratories, Chicago.

1. Bryer, M. S.; Schoenbach, E. B.; Ott, C. E., and Long, P. H.: The Experimental Pharmacology and Effectiveness of 3-4, Dimethyl-5-Sulfanilamido-Isoxazole, Bull. Johns Hopkins Hosp. **82**:633 (June) 1948.

2. Sarnoff, S. J.: Studies on 3-4, Dimethyl-5-Sulfanilamido-Isoxazole (Nu-445) in Humans, Proc. Soc. Exper. Biol. & Med. **68**:23 (May) 1948.

Rhoads and his co-workers [3] treated 24 adult patients, giving the drug alone to 14 of them and in combination with penicillin or streptomycin to 10. There were 6 patients with meningitis (meningococcic 3, pneumococcic 2 and of undetermined origin 1), 6 with urinary tract infections, 5 with infections of the respiratory tract, 1 with erysipelas, 1 with scarlet fever and 4 with postoperative infections. Two patients with meningococcic meningitis treated with the drug alone recovered. Blood levels of the drug after daily doses of 4 to 6 Gm. averaged 9.1 mg. per hundred cubic centimeters. About 30 per cent of the drug was found in the acetylated form. Urinary excretion accounted for slightly more than 60 per cent of the amount given. There were 4 reactions in these 24 patients, 1 of generalized dermatitis, 1 of crystalluria and hematuria and 2 of nausea and vomiting. Haines and Miceli [4] treated 8 adults with Proteus vulgaris urinary tract infection. In 5 there was reversal of the urine culture, in 2, no reversal of the culture but clinical improvement and in 1, no change. No toxic reactions occurred. Narins [5] treated 50 patients with urinary tract infection due to Escherichia coli and/or P. vulgaris. With an 8 Gm. daily dosage there were 57.9 per cent of the former cured and 44.1 per cent of the latter cured. Save for 2 patients, each with dermatitis and nausea, the drug was tolerated with no ill effects. Neutropenia and crystalluria did not occur.

Eighty-two patients with urinary tract infections were treated by Carroll, Allen and Flynn.[6] They obtained no evidence of the development of increased resistance on the part of the organisms studied to gantrisin,® which was in contrast to their experience with other sulfonamides and with streptomycin. It was the drug of choice in treatment of urinary infections due to P. vulgaris and E. coli. Svec, Rhoads and Rohr [7] used this drug for 300 patients for a variety of conditions without the development of renal complications. Ninety per cent of the drug is excreted in the urine in forty-eight hours after a single dose, the most rapid excretion occurring in the first eight hours.

3. Rhoads, P. S.; Svec, F. A., and Rohr, J. H.: Laboratory and Clinical Observations on the Use of a New Sulfonamide—3-4, Dimethyl-5-Sulfanilamido-Isoxazole (NU-445), Proc. Central Soc. Clin. Research **20**:68, 1947.

4. Haines, W. H., and Miceli, S.: Some Observations on the Management of B. Proteus Infections of the Urinary Tract, Pennsylvania M. J. **50**:1328 (Sept.) 1947.

5. Narins, L.: The Treatment of Bacillus Coli and Bacillus Proteus Infections of the Urinary Tract with a New Sulfonamide (NU-445), J. Urol. **59**:92 (Jan.) 1948.

6. Carroll, G.; Allen, H., and Flynn, H.: Gantrisin® in the Treatment of Urinary Infections, J. A. M. A. **142**:85 (Jan. 14) 1950.

7. Svec, F. A.; Rhoads, P., and Rohr, J.: A New Sulfonamide (Gantrisin®): Studies on Solubility, Absorption and Excretion, Arch. Int. Med. **85**:83 (Jan.) 1950.

Because of the high rate of solubility and the low incidence of toxicity, this sulfonamide preparation was used alone in the treatment of 71 children entering the Children's Memorial Hospital with various types of infections. As can be seen in the table, the response was

Summary of Response of Infants and Children to Gantrisin®

Number of Children	Diagnosis	Number with Good Response	Number with No Response	Results of Cultures
7	Lobar pneumonia	7	..	3 Pneumococcus 2 Staph. aureus 1 N. catarrhalis 1 Mixed: Str. viridans; Str. hemolyticus
6	Bronchopneumonia	6	..	1 Pneumococcus 1 Str. hemolyticus 2 Staph. aureus 1 Str. viridans 1 No culture
3	Atypical pneumonia	..	3	3 No cultures 1 Negative cold agglutination reaction
8	Bronchitis	8	..	1 Nonhemolytic streptococcus 4 Mixed: Str. viridans; Staph. aureus hemolyticus; Str. hemolyticus 3 No cultures
3	Otitis, suppurative	3	..	1 Pneumococcus 2 Staph. albus
9	Otitis	9	..	6 Staph. aureus hemolyticus 2 Str. hemolyticus 1 Nonhemolytic staphylococcus
19	Tonsillitis	19	..	6 Str. hemolyticus 4 Staph. aureus hemolyticus 1 Str. viridans 1 N. catarrhalis 1 Pneumococcus 1 Nonhemolytic streptococcus 5 No culture
5	Cervical adenitis	5	1 Incised	1 Str. hemolyticus 4 Mixed throat: Staph. aureus hemolyticus; Str. hemolyticus; Str. viridans; H. influenzae; pneumococcus
4	Urinary infections	3	1 Nonhemolytic streptococcus	1 P. vulgaris 2 E. coli
7	Miscellaneous	4	3	Dacryocystitis; pneumococcus

excellent in all but 7 patients. Of the latter, 3 were thought to have atypical pneumonias, 1 nonhemolytic streptococcus pyuria, 1 rheumatic fever, 1 infectious mononucleosis and 1 exanthema subitum.

SUMMARY OF CASES

Lobar Pneumonia.—The ages of these patients were from 10 months to 10 years. At the onset of therapy the temperatures were 102 to 105 F. These returned to normal in twenty-four to forty-eight hours and remained so.

Bronchopneumonia.—The temperatures of these 6 patients, aged 2 to 5 years, were 102 to 104 F. when administration of the drug was started and became normal after twenty-four to forty-eight hours.

Atypical Form of Pneumonia.—Two of these children, both 10 years of age, had what appeared to be a virus pneumonia, with a temperature of 105 F. in one and of 103 F. in the other. The white blood cell counts were 10,000 in both children, and the roentgenograms, physical findings and clinical courses were suggestive of the presence of a virus infection. Both showed no improvement after three days of gantrisin® therapy, with blood levels of 12.7 and 10.2 mg. per hundred cubic centimeters. They were given penicillin, 30,000 units, every three hours intramuscularly. With this therapy the temperature returned to normal in six days in one child and in three days in the other, indicating little effect with penicillin.

The third patient was a 5 year old boy who had no fever but who had a pulmonary consolidation which was thought to be tuberculous in origin. He had had a recent positive Mantoux reaction. The drug was used for three days with no improvement in his condition. The blood level of the drug was 6.4 mg. per hundred cubic centimeters. Smears of gastric washings and guinea pig inoculations were negative for tubercule bacilli. The patient was discharged from the hospital after three weeks with no change in his pulmonary findings.

Bronchitis.—There was clinical and physical evidence of pulmonary infection but negative roentgenographic findings in 8 patients. These 8 children, ages 13 months to 5½ years, had temperatures of 101 to 102 F. at the onset of therapy. They became normal in twenty-four to thirty-six hours.

Otitis Media.—Eight children, 7 months to 6 years of age, had temperatures of 102 to 105 F. at the time medication was begun. The other child with acute otitis media had a normal temperature during the entire course of his illness. The elevated temperatures returned to normal in twenty-four to forty-eight hours. Paracenteses were not performed. Suppuration was present in 3 children before the institution of therapy and subsided within one week.

Tonsillitis.—All the 19 children had moderate to severe infection of the tonsils or the throat. The ages varied from 9 months to 11 years, with temperatures of 101 to 105 F. at the start of therapy. These patients were free of fever in twelve to twenty-four hours.

Adenitis.—There were 2 children with inguinal adenitis, 2 with cervical adenitis and 1 with axillary adenitis. The nodes were large and tender. The ages of the patients were 2 to 9 years, and their temperatures were 101 to 102 F. The temperatures returned to normal in twelve to thirty-six hours, with complete subsidence of the infection without suppuration or surgical intervention in 4 of the children. Surgical incision was necessary in 1 child with cervical adenitis.

Urinary Tract Infections.—Three children in this group, aged 2 to 5 years, with temperatures of 101 to 104 F., had rapid subsidence of both fever and pyuria. Urine cultures became negative for pathogens. In the fourth patient, gantrisin® was used without effect on an infection due to a nonhemolytic streptococcus.

Miscellaneous Infections.—These consisted of an alveolar abscess in a 10 year old child with a temperature of 101 F., acute bursitis with heat and redness in a 9 year old boy without fever, an extensive infected burn in a 6 year old child with a temperature of 103 F., an undetermined infection in a 5½ month old infant with an esophageal atresia and a temperature of 103 F. and pneumococcic dacryocys-

titis in a 6 month old infant. The temperatures remained normal after twenty-four to forty-eight hours of therapy. One child with infectious mononucleosis, 1 with rheumatic fever and 1 with exanthema subitum did not show any response.

Approximately 50 other infants and children have also received gantrisin® in combination with penicillin and streptomycin. In 4 of these children being treated for influenzal meningitis with streptomycin and sulfadiazine, blood appeared in the urine within twenty-four to forty-eight hours. Administration of the sulfadiazine was discontinued, gantrisin® was substituted and its use was continued for two weeks. The red blood cells disappeared from the urine and normal recovery occurred.

CULTURES

Cultures taken on this group of children showed no variations from those of other children seen at the same time but being treated with other drugs. In most instances when cultures of material from the throat were taken, such as in pneumonia, throat infections, bronchitis, cervical adenitis and nonsuppurative otitis media, only the predominating organism is listed in the table unless a variety of organisms was present with none predominating.

DOSAGE

The gantrisin® was supplied in 0.5 Gm. tablets for oral administration. The usual dosage was 1 to 1½ grains per pound (0.13 to 0.19 Gm. per kilogram) of body weight divided into four to six doses daily. A few children were given as much as 2 grains per pound (0.26 Gm. per kilogram). The initial and sometimes the second dose was doubled on the first day of therapy. Administration of the drug was continued for three to ten days. No alkali was given. In no instance was there a recurrence of the infection.

REACTIONS

In the combined group of the 71 patients and the 50 other children whose responses are not included in the table, no reactions were present that could be attributed to the drug. One child with lobar pneumonia and a temperature of 104 F. took the drug poorly the first few days. In another there was some nausea the third day but no vomiting. Crystalluria and hematuria did not occur. There were no changes in the red blood cell count or in the hemoglobin concentration. In no instance did a leukopenia develop, although in the 9 year old boy with inguinal adenitis, lymphangitis of the leg and a temperature of 102 F., the white blood cell count was 3,000, with 40 per cent polymorphonuclear cells and 60 per cent lymphocytes, twenty-four hours after his admission and the start of therapy. Unfortunately, another count was not obtained before his discharge. It was felt that the leukopenia occurred with his infection rather than with the administration of the drug. No secondary rise of temperature occurred during medication up to ten days.

BLOOD LEVELS

With the usual dosage of 1 to 1½ grains per pound daily, the blood levels varied from 3 to 15.7 mg. per hundred cubic centimeters. The average blood level was 6.4 to 10.7 mg.

COMMENT

Gantrisin,* given to the 71 children and infants with infection, gave results comparable to those of the other sulfonamides, such as sulfathiazole, sulfadiazine and sulfamerazine, that we have used in treatment of like infections. Administration of alkalis did not seem to be necessary and reactions did not occur.

Neither crystalluria, nor red blood cells, were ever found in the urine.

707 Fullerton Avenue (14) (Dr. Bigler).

AN APPROACH TO PSYCHIATRIC PROBLEMS IN CHILDHOOD

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THE ATTEMPT in this paper is to provide the physician with a viewpoint and a general approach to the psychiatric problems of childhood.[1] The physician may regard much of what is outlined here as only common sense. This is probably true, for the endeavor in child psychiatry is often only the conscious application of common sense principles to the difficulties parents and children encounter in living with each other. In this field the development of a point of view regarding the individual person in his relationships with other persons is more important than the specific technics used in dealing with his emotional problems. In addition to an adequate consideration of his physical state, this involves greater attention to what goes on in the person's emotional life. It perhaps involves a greater stress on states of feeling than on thought processes. It tends to regard even intellectual processes, that is, the thoughts and ideas which a person expresses, as manifestations influenced to a variable extent by his emotional attitudes.

We have often heard criticism regarding the actions of a person in terms of "He should not do so and so, because he knows better than that," implying that he has sufficient intellect to use better judgment. The error in this is that a person's actions are more influenced by how and what he feels than by what he knows and how well he thinks. Even the ability to think or to acquire knowledge, it is now known, is to a great extent influenced by the person's state of feeling. A person's state of feeling may be such that he is unable to act on a rational judgment which his intellect has reached.

Essential to the understanding of the psychiatric problems that occur in children is an adequate conception of the nature of the psychologic growth and development of a child from birth until biologic maturity. This requires a recognition of his emotional and physical needs at various periods of growth, as well as a knowledge of his capabilities at these times. In order for relatively satisfactory emotional

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1. Many of the concepts presented were in part derived from Isaacs, S.: The Psychological Aspects of Child Development, London, Evans Brothers Ltd., 1935.

development to occur, it is necessary that the total needs of the child be met adequately. These needs include not only the various nutritive substances which the child requires for his metabolic functions but also the opportunities for interreacting with one or more persons at different periods in his development in a manner which will comprise for him a series of satisfying emotional experiences. The opportunities for the exercise of his capacities as they develop, i. e., to do things for himself and others, are an essential aspect of such experiences.

DEPENDENCE VERSUS INDEPENDENCE

The nature of the developmental period of the individual person is best understood in terms of two biologically determined forces operating within him. One of these forces is constituted by his tendency to be dependent. This is determined by the degree of his helplessness to satisfy the need for nourishment, warmth and protection from threatening environmental circumstances. The other is constituted by the striving for independence which increases with his capacity to satisfy the aforementioned needs through his own efforts. There is a constant interplay of these two forces throughout the developmental period of the person. Their specific manifestation depends on the age period, the inherited somatic equipment, the integrity of the organism, its state of health and the pattern of intrafamilial relations in a given society. In a way, one could look on the growth and development of the child as a drama in which the tendency to be dependent and the striving for independence are in a constant struggle of varying severity. It is easy to see simple manifestations of this drama. In the very young child one may often see an insistence beyond the usual age on drinking milk through a nipple and at the same time an equal insistence on his own handling of the spoon with which he is fed more solid foods. Later, the child may demand independence in walking, but at the first contact with a new or seemingly threatening situation he will reach for his mother's hand or hold onto her skirts.

The latter example is the prototype of the phenomenon to which, when it occurs later in life and to a more pronounced degree, psychiatrists apply the term regression. This merely refers to the fact that when the person is confronted with situations strongly threatening to his security, he often tends to revert to forms of behavior which were associated with periods of greater security. This, to some extent, may explain some forms of enuresis, e. g., the recurrence of bed wetting at the birth of a sibling, as well as some instances of persistent thumb sucking. Each physician can probably elaborate from his own experience other examples illustrative of the interplay of dependent needs and independent strivings. At this point it can be said that the emotional development of the child is determined by how and to what extent his

dependent needs are gratified and to what extent he is provided with opportunities for the expression of his strivings for independence.

The human infant probably has the most prolonged period of helplessness of all newborn in the animal kingdom. For a long time after birth he is completely dependent for the satisfaction of all his basic biologic needs on his mother. Though the physician is accustomed to think of the growth rate in infancy and childhood as being extremely rapid, he needs to remember that, in comparison with that of other animals, the rate of growth is extremely slow. Even as the child grows and gradually is capable of doing more and more things for himself, there continues to be a relative dependence on the parents. It must also be kept in mind that the period of relative dependence varies with the culture into which the child is born. In some cultures a child is able and is expected to care for most of his needs by early adolescence. In other cultures, specifically our own, dependent on economic and social factors, the period of relative dependence often continues even past adolescence. It is within the basic pattern of dependence on the parents and slowly increasing independence that the emotional development of the child occurs. It might also be stated that most, if not all, of the emotional problems which occur in children have their roots in the dynamic relationship of these two forces as they operate within the parent-child constellation.

During infancy the child has all his needs met by the mother and receives most of his sensual gratification from her, but even during this period important changes tending toward independence begin to occur. Among these are weaning and the addition of solid foods to the diet. Later, the child begins to walk and thus to move about over a wider area. He begins to acquire the basic rudiments of speech and thus to have a greater possibility of communication with others. In early childhood this development continues and the child begins to learn more about the world, which still largely comprises only the family. During this period, his emotional life involves chiefly parents and siblings. At this time he learns about more aspects of his relationship to the family and this involves for the first time the need to inhibit certain forms of behavior. It is at this point that toilet training may be started. Now he begins to learn that there are certain things he cannot do to other persons and to objects in his environment.

In later childhood another important development occurs. He becomes aware of a world outside the four walls of his home. He becomes aware of other children who are not his siblings, as well as of other adults who are not his parents, yet who may have a controlling influence on him. A great part of his interest and energy is diverted toward persons outside the immediate family. The family, however, continues to be the center of his world and all his experiences, including

those outside the family, are related to what occurs in the home. From this time on, the child begins to get more and more of his emotional satisfactions in relation to persons other than his parents, particularly through other children of his own age, both individually in the form of close friendships and collectively in the striving for acceptance and status within the group. This is especially evident during the preadolescent and adolescent periods of development. During the latter, there is an increased pressure of the sexual impulse which extends the positive (affectional) interests of the person to members of the opposite sex. All this tends to a greater independence of the home. He is now able to satisfy many of his needs independently of his parents and obtains an increasing number of important gratifications outside the family. The period during adolescence when the person becomes relatively independent of his parents and his family varies with the social system in which he develops. Generally speaking, this tends to occur earlier the more primitive the culture. As stated previously, in our own culture it tends to take place relatively late; in individual instances, even beyond the technical limit of the adolescent age period.

EFFECTS OF ENVIRONMENT

Up to this point attention has been focused chiefly on the development of the child. Now more specific attention must be given to the environment in which this development takes place. It is in the dynamic constellation of father, mother and siblings in our society that the child encounters his most significant experiences in obtaining satisfaction for his dependent needs and in exercising his drive to greater independence. Parenthetically, I should emphasize the point that the family is a dynamic constellation in a persistent state of flux, influenced by a culture which is equally dynamic. The physician is dealing with a situation in which there are few constants, thus tremendously complicating his efforts to understand the basic relationships and how they operate. For any given period in history, however, even our own, the rate of change in the family and the culture is sufficiently gradual to make it possible to draw relatively valid conclusions regarding the basic relationships. In any event, the biologic needs of the person do remain constant from generation to generation, even though the manner and form (culture) in which these needs are met may change. A child needs food, warmth and affection, regardless of how and by whom these needs are satisfied. Furthermore, a child needs the opportunity to exercise his increasing maturity, regardless of the changing social forms through which this maturity may be expressed. In our culture this is accomplished primarily within the family. Schools, clubs and camps attended at the appropriate time can really be looked on as extensions of the family function. In addition to father, mother

and siblings, teachers, classmates, playmates, club leaders and others entering into the child's life also need to be considered. The ways in which the child's basic needs are met will depend on the emotional state of the persons who influence his life.

The chief emphasis needs to be on the parents, since they are the ones with whom the child comes in contact initially and with whom he continues to maintain the most intensive, as well as the most prolonged, relationship during his formative years. How the parents meet the basic needs (dependent-independent) of the child will depend on their emotional state, which in turn has been determined by how adequately the needs of each parent were met during his or her childhood. In other words, the degree to which the parents will be able to perform their function adequately will depend on the degree to which their needs were satisfied during their own developmental period. This determines the extent to which they will be free from disabling emotional problems. A relative degree of freedom from the latter tends to create an atmosphere in which there is an absence of long-lasting tensions and anxieties, thus permitting the parents a relaxed expression of positive feelings toward each other and toward the growing child. This does not imply that the ideal environment is some mythical paradise in which there is never a harsh or unkind word. What I am trying to convey is a more reasonable objective, a situation in which mutual affection and respect exist among members of the family and feelings can be expressed without anxiety and reasonable demands can be made without guilt. Such an environment would provide the optimum conditions for the healthy development of the child. He would be permitted the opportunity, when ready, for the exercise of his independent strivings, and at the same time the parents would provide without hostility or guilt the firm discipline necessary to guide his development toward an acceptable social adjustment.

SOURCES OF DISTURBED PARENT-CHILD RELATIONS

What has been said thus far stresses that emotional problems in children occur when something has gone wrong in the relationship between the child and his parents. This is most apt to occur early, but it can and does occur during any period in the development of the child. There are certain well known events in the child's development during which the disturbed relations between the child and his parents may become more apparent and may be manifested by symptoms most evident in the child. In this sense the child is a delicate barometer reflecting the state of feeling within the family. In fact, in dealing with psychiatric problems in children, it is probably valid to conceive of the symptoms in the child as expressing the "pathology" within the family (the disturbed child is a symptom of disturbed family relationships).

In many instances the difficulties in the child become clear only when the conflicts within either one or both parents begin to be understood. In a striking instance of such a relationship, a child was referred to the clinic because of a complaint by the school that he was unmanageable. He fought with the other children and often attacked them physically. The school tended to blame the parents, whom they accused of a lack of interest in their child's adjustment in school. On the insistence of the school, the mother, somewhat reluctantly, participated in a program of therapy at a child guidance clinic, and it was only after a fairly prolonged period that her own anxieties in regard to discipline became fairly well defined. She herself had been a subdued, extremely compliant child who had never been able to assert herself with her parents or siblings. She suffered from a feeling that she had been neglected, had been the "ugly duckling" of the family and had not received the affection from the family that she wanted. She felt that her submissive, compliant attitude had gone without due reward. She resented an older brother who was much more aggressive, the "black sheep" of the family, and who received far more affection from her parents. This persistent feeling was reflected, therefore, in her attitude to her own child; on the one hand, she wanted him to be well liked, which to her meant submission, but, on the other hand, she did not want him "to be taken advantage of," as she felt had been true in her childhood, which meant aggression and defiance. This ambivalent attitude on her part was reflected in her daily management of problems of discipline with her son and was expressed in her uncertain and contradictory attitudes which were sensed by him. Her own conflict was concisely and dramatically revealed in a statement she made to her son when called on by the school to discipline him for having bitten another child. She reprimanded him with, "Why did you bite so hard?"

It would be easy for one to take a judgmental attitude toward this woman, label her as a weak mother and perhaps attempt to urge her to be firmer in her discipline. It is probable that in many instances such an attitude would be ineffective and probably would only serve to increase her feelings of inferiority and tend to arouse her passive antagonism. Furthermore, the nature of the problem in the child begins to become clear and understandable in etiologic terms only when this mother's own problem is comprehended. This further leads to a therapeutic approach which necessarily would include helping this mother with feelings which have persisted from her childhood to the end that she will be able to take a more positive attitude in her role as a mother.

During the first year or two of life the child's main contact is with the mother; his basic needs are satisfied by her. Still, the importance

of the father in completing the family constellation, in the emotional atmosphere established with the mother and in providing the basic security of the family unit cannot be overemphasized. In fact, it is too often true that, even in good clinics for dealing with behavior problems in children, the role of the father in the situation is not adequately considered or properly evaluated. Though in much of what follows I shall often refer chiefly to the mother, I do not thereby ignore the importance of the father's role within the family.

Infant Feeding.—The earliest and perhaps the most important relationship between mother and child occurs in feeding. The biologic importance of this is obvious, but its psychologic importance is frequently not considered at all or is insufficiently stressed. The physician is apt to look on infant feeding largely as a physiologic process in which only the child need be considered and the mother is an incidental, though often a useful, mechanism for this purpose. Many times the attitude of even the well trained physician and pediatrician is as though the feeding of the infant could be better accomplished not only by a carefully calculated formula but also by the administration of the formula without the intervention of human hands, through some sterile mechanical means. In fact, during one phase of pediatric thinking regarding child development that was in a sense the ideal aimed at. An oversimplified mechanistic conception of stimulus and response seemed to be the guiding principle. This principle has now been largely discarded.

At present the physician is aware of the importance of feeding, not only in terms of weight, vitamins and calories but also as a significant life experience which is important in the emotional development of the child. He now thinks of it as offering the child his first interpersonal relationship. Through the feeding experience the basic pattern of the relationship between the mother and the child becomes established. This is mediated through the developing sensory apparatus of the child: touch, smell, taste, kinesthetic sensation, sight and sound. Most important are the pleasurable sensations about the lips and mouth which the child receives while nursing. Anything that may interfere with the child's ability to ingest pleasurably adequate quantities of food, as in the case of an infection in the mouth, threatens his organic integrity. This can also be expressed in psychologic terms as a threat to the child which produces anxiety and which, if prolonged, may adversely influence his emotional development. This emphasizes the fact that there may occur factors within the child, such as disease or physical handicap, which, quite apart from familial relationships, can affect his psychologic development. Perhaps even here it is incorrect to separate disease conditions from the general attitude of the mother toward the infant. Most physicians are aware of the influence of the emotional state of the mother on the emotional state of the child. Often

a mother in giving a history will relate a period of irritability, poor feeding and bowel disturbance in an infant with her own disturbed emotional state at about the same time. Most pediatricians at present recognize that the investigation of problems in infant feeding involves a consideration not only of formulas but also of the attitudes of the mother and even of the relationships within the family.

Ribble [2] argued the importance of this point of view in summarizing her studies on feeding difficulties in infants. In the genesis of these difficulties, she stressed the decisive influence of that quality in the mother-child relationship which she called "mothering." She suggested that such problems often occur when the infant does not receive adequate physical handling and other forms of affectionate attention which she included in the term "mothering," and that when this is supplied the condition usually subsides or is ameliorated. When the lack of "mothering" (a term I must use for lack of a better one) is prolonged, permanent effects on the personality development of the child may remain. One of her cases is illustrative. An infant's mother died shortly after childbirth and the infant for various reasons had to remain in the hospital for several months. During this time, the members of the nursing staff paid much attention to him and the child flourished, developing at a more rapid rate than other infants in the ward. Since there were no relatives to claim him, the child was placed in a good orphanage. The amount of attention diminished greatly and definite changes were noted, such as poor feeding, pallor, loss of skin turgor and irritability. Later there developed apathy, a tendency to sleep more than the normal amount and persistent diarrhea. When he was given increased personal attention, the symptoms quickly subsided. It seemed, however, that a lasting effect on the child remained, because later, after he was placed in a good foster home, when separated from the foster mother for even one day, he reacted with loss of appetite, refusal to eat and intestinal disturbances.

Much more could be said about the psychologic aspects of infant feeding. It would all tend to emphasize the importance of the emotional state of the mother and of the relationships within the family in the origin of such problems. At one time the emphasis was on regularity of schedules and quantity of feedings. This often did not consider individual differences among infants, frequently producing anxiety in mothers which proved deleterious to their relationship with the child. The current tendency is in the reverse direction, exemplified by "demand feeding!" Though indicative of a more desirable attitude and on the whole conducive to better relations between mother and child, it does not obviate the need to consider the mother as an individual person.

2. Ribble, M. A.: The Rights of Infants: Early Psychological Needs and Their Satisfaction, New York, Columbia University Press, 1943.

As one pediatrician expressed it, the rigid, compulsive mother who formerly worried about schedules and now conscientiously applies the "demand feeding" principle may just as compulsively, with equally deleterious results, ram a nipple in the infant's mouth every time he cries.

The Weaning Period.—The next important period during which a conflict situation may develop between the infant and his mother is at weaning. What occurs at this time between the mother and the child will greatly depend on the relationship already established during the nursing period. If the relationship between the mother and the child has become disturbed during that period and the disturbance has not been adequately resolved, difficulties will probably continue in relation to weaning. It should be stated that in all families some emotional problems probably will occur, in both the mother and the child, in the growth of their relationship to each other. In most instances the conflict between them is adequately resolved with few, if any, long-lasting emotional residuals. It is only when these conflicts are not resolved and continue on in one form or another that lasting emotional disturbances may occur. In many instances, a mother's attitude toward weaning is determined by what she has heard from mothers or learned from inadequately digested books or lectures. She may have developed a rigid attitude toward weaning and may feel compelled to carry it out in an arbitrary fashion. In such instances, a general practitioner or a pediatrician who can reassure the mother regarding the individual differences in children and who can help her to feel less anxious about weaning may be of decisive help in resolving such a conflict.

In addition to understanding the mother's attitudes regarding weaning, it is also necessary to recognize what the child may be expressing by his reluctance to give up his nursing. In some cases this may merely be a reluctance to relinquish an experience that has proved to be pleasurable. Such a feeling may be gradually overcome by the mother, provided she does not insist on immediate results and is able to give the child emotional satisfaction by other pleasurable interpersonal experiences. In some instances a stubborn reluctance to give up nursing may be indicative of extreme insecurity in the child and indicative as well of an equally disturbed emotional state in the mother, which may require some resolution before weaning can be successfully accomplished. For similar reasons problems may occur at this period in regard to spoon feeding, cup feeding and the introduction of solid foods. I can only emphasize that in this, as in all other branches of medicine, the physician should look first for the simplest etiologic factors before going on to the investigation of more complicated causes.

Toilet Training.—Another important event in the child's life over which a conflict may occur between the mother and the child is when toilet training is undertaken. The same considerations that were

pointed out in regard to feeding and weaning also hold true here. The conflict between mother and child over habits of cleanliness may manifest itself long before the child is able to express his defiance verbally.

In 1 case, the child, when placed on the toilet, seemed outwardly eager to comply with the mother's wishes. Somehow nothing happened, until the mother, tired of waiting, removed him, and the child almost promptly had a bowel movement in his trousers. Another child would fail to have a bowel movement when placed on the toilet but later would deposit his movement in a corner of the bathroom and then with some anxiety call his mother's attention to it. This mother could rarely allow herself to get angry at the child and, even in these circumstances, would ask the child to clean up with only a minimal expression of irritation. The child always complied immediately with the mother's request, but the pattern continued.

Because of our cultural attitudes toward cleanliness, the struggle over toilet training may be particularly severe and often results in long-lasting emotional conflicts between the mother and the child. At one point, pediatric attitudes toward toilet training, as toward feeding, were rather mechanistic and somewhat rigid. Early toilet training was emphasized and many conscientious parents developed extreme anxieties in their efforts to carry this out. At present, the pediatrician is more inclined to take a tolerant view regarding toilet training, to consider individual differences in the rate of maturation and to suggest to the parents that they themselves observe and judge the child's readiness for training. Errors are as possible, however, in the direction of too great leniency in this matter as the reverse, so that in some rare instances one may find parents who, misinterpreting present trends, will make no attempts at toilet training, and a child may go as long as four or five and even six years without any effort having been made at accomplishing this.

Preschool and Early School Period.—The preschool and early school period is another time that problems may occur or become exacerbated. At this time, the child begins to acquire interests outside the family. He shows a more continued interest in other children and in some instances may have the opportunity to express this in nursery school, where he obtains prolonged contact not only with children but also with other adults. At this time much of his activity can be described as explorative in nature. He usually is fairly active and begins to test more energetically than heretofore the limits of what he can and cannot do. There are more obvious strivings for independent activities and the parents are faced with the problem of where and how to set limits. Where previously the child generally reacted to the parents as though they were omniscient and omnipotent, he now expresses more frequently and more definitely his growing doubts regarding their power and wisdom.

This may be manifested by increasing acts and expressions of defiance. He may object to his usual bedtime and compare this with what may be required of a playmate. The same comparisons will occur in regard to other aspects of his life important to him, such as food, clothing, privileges and play equipment.

If the basic relationship between the child and the parents has been good, in the sense that there have been mutual affection and respect, based on easy communicability, it is not likely that any serious problems will occur. If, however, the intrafamilial relationships are disturbed and there is a conflict, not only between the parents and the child but between the parents themselves, then such disturbances are apt to be accentuated by the problems presented at this time, and the problems tend to be magnified by the conflict. To the disturbed parents, the matter of instituting limits in the child's behavior is often associated with extreme anxiety. Because of their own disturbed feelings, the mother, as well as the father, may feel ambivalent about specific disciplinary measures and may have a sense of guilt in the administration of discipline.

An instance of this ambivalence is shown by the following case: A family was entertaining a large gathering of friends. The parents put their 4 year old child to bed at the usual time, but the child, aware of the approaching party, expressed reluctance to go to bed and finally began to cry. The mother, irritated by the child's insistence and the crying, finally spanked her. At this point the child's crying increased and the mother, suddenly feeling guilty, took her into her arms to soothe her and ended by taking her downstairs and allowing her to remain with the gathering for several hours past her bedtime. In working with this mother, it became fairly evident to the psychiatrist that the mother, in spanking the child, had sensed at the time that much of the irritation which she was expressing toward the child and under the influence of which she had spanked her did not relate only to the specific incident but to other, more general, negative feelings she had toward this particular child. This caused her to react to what she had done with guilt, just as if she had made an excessive requirement of the child and had punished her unjustly. This made her waver in a disciplinary act that, on the basis of the actual circumstance, could have been considered reasonable.

Problems of this sort are relatively frequent among parents, not only at this age period of the child but throughout the developmental period. One frequently sees parents who are uncertain about their role in respect to problems of discipline. One cannot deal with these problems in practice merely by an academic discussion of principles of discipline, as, for example, whether to spank or not to spank, whether to be strict or lenient, but one has to be concerned primarily with the parental attitudes, the states of feeling and the emotional tone of the relationships

within the family. Thus, when a parent inquires of a physician whether spanking is good or bad for a child, the answer cannot be merely "yes" or "no," since such an answer does not take into consideration the aforementioned factors. It may clarify the issue to consider that a spanking or any other disciplinary measure, such as curtailment of privileges, may be less disturbing to a child than a harsh word or merely a hostile silence. This observation should not be interpreted as expressing approval or disapproval of spanking or of any specific disciplinary measure. It is important to realize that it is not the specific measure or measures used but the emotional state and attitude of the parents toward the child and his behavior which are decisive.

Other Important Periods.—It is possible to refer only briefly to other important periods which involve changes in the child's relationship to his family and in which emotional problems within the family may become exacerbated. Such another period is the time when the child enters school. At this time, and to a greater degree during the preadolescent period, the child tends to focus an increasing amount of his interest outside the home. Correlated with this is a more rapid maturation of the organism which continues through adolescence, most prominently marked by the development of the secondary sex characteristics and accompanied with an apparent accentuation of sexual drives with all their manifold psychologic manifestations. The parent may now become quite anxious about sexual curiosity and even forms of sexual experimentation. There may also be present within the parent an unconscious resistance to the manifestations of increasing maturation and independence which may carry over into the adolescent period, when the parent and the child have the mutual problem of achieving independence of each other, in a sense, the problem of cutting the psychologic umbilical cord. Again the physician must keep in mind that here, as in other periods of development, he can expect a certain amount of emotional turmoil in most cases, but, if the general development up to this point has fulfilled the conditions of providing the child with adequate satisfaction of his dependent needs and of giving him the opportunity for the expression of his independent strivings, and if the parents are not too ambivalent about the child's increasing independence of them, the difficulties will probably be mild and transient. In instances in which these conditions have not obtained, more lasting disturbances may occur. It is at this period in life that many of the serious emotional disturbances which may continue on into adulthood often become manifest.

MANAGEMENT OF SPECIFIC PROBLEMS

Nothing specific has been said about problems such as enuresis, temper tantrums, phobias and the entire conglomeration of behavior disturbances with which the physician is faced. The physician, daily

confronted with anxious and urgent parents, limited in the time he can devote to an individual case, would like a specific from the psychiatrist. He would like to be supplied with a technic that he can then successfully apply to the treatment of such problems and thus avoid the sense of inadequacy he too often feels in trying to help parents. Unfortunately, the psychiatrist has neither specifics nor simple formulas. He can talk only in terms of interpersonal relationships, states of feeling, attitudes, emotional tensions and resolution of conflicts, all of which may seem vague and nebulous to the pragmatically oriented physician. Yet, it is only through the approach represented by these terms, slow and difficult as it may be, that these problems become comprehensible and possible of solution. The child psychiatrist emphasizes that the specific behavior disorder is only a symptom of an underlying psychopathologic state and must be regarded as one would a cough or a headache. Furthermore, the psychopathologic state is conceived as being present not only with the child but also in the character of the relationship between the child and his parents and often in that between the parents as well. In brief, the important factors are to be found in the intrafamilial relationships. Finally, in order to understand the intrafamilial relationships, the physician needs to pay attention to the emotional problems within each of the units, father, mother and child, which comprise the family constellation. From the therapeutic standpoint, therefore, the problem of the physician in dealing with such situations in his practice is much the same as that with which he is confronted in other aspects of medical practice. He needs to determine the nature and severity of the disturbance within the family and then decide what he is able to offer in therapeutic skill and the time required to exercise this. With a proper conception of the nature of these problems and the dynamic factors involved, many of them can be solved fairly adequately in the average general practice. Many such problems can reach a beneficial resolution with a moderate expenditure of time and with a modest amount of experience in psychotherapy. In dealing with these problems, the physician also needs to know how he can make the best use of auxiliary professional skills, such as those offered by a clinical psychologist, or the services rendered by a medical or psychiatric social worker. He also needs to determine when the difficulties within the family are of such severity that they require the more intensive and prolonged management rendered possible by the services of a psychiatrist or a child guidance clinic.

THE THERAPEUTIC ATTITUDE

In most of what has already been said, the desirable therapeutic attitude to psychiatric problems in children is indicated. In attempting to solve these problems, many physicians have paid attention mainly to the child. The parents have sometimes not been considered at all or

have hovered in the background as more or less shadowy figures who were criticized for the difficulty and given specific instructions on what to do and how to behave in the future. In these circumstances, the parents, while outwardly submissive and compliant, often inwardly felt either neglected or attacked and have gone away from the consultation apparently subdued and obedient but in some cases angry and openly defiant. It would probably be desirable, particularly in the short contacts possible in general practice, that the main therapeutic orientation be toward the parents. It would be beneficial for the physician not only to consider them as parents and from this standpoint to evaluate their relationship to the child but in addition to consider them as individual persons with their own unique emotional problems.

There are a number of attitudes on the part of the physician which he may unconsciously assume toward the parents and the child that may diminish his usefulness in helping them or which may even exacerbate an already tense situation. The physician may have a critical attitude toward the parents that only increases their anxiety and their sense of failure and at the same time creates in them a feeling of defiance. It is important for the physician to keep in mind that parents who consult him regarding behavior problems in their children are often already frightened and already overly self condemnatory. The physician might tend to assume an authoritarian, somewhat dictatorial role in which he orders the parents to behave in a way which, at that time, may be psychologically difficult, if not impossible. Along these same lines, when pressed by parents, he may be tempted into assuming an omniscient attitude and offer advice on which the parents are unable to act because of their own unresolved emotional problems. Another danger is the tendency for the physician to overidentify himself with the child and to think and act in the erroneous terms of the good child versus the bad parents. Finally, one may inadvertently be trapped by one or both parents into taking sides in a family conflict.

Perhaps the one most important quality for the physician to acquire in developing a simple but effective psychotherapeutic approach is the ability to listen. In many instances, the best medicine a physician can offer to a patient is fifteen or twenty minutes of attentive listening. If, in doing so, the physician can achieve an attitude that is noncritical and, through an empathic sense of their difficulties, can help the parents express their own anxieties, uncertainties, feelings of guilt and other feelings for which they already condemn themselves too severely and about which they are already too ashamed, he would tend to diminish the surcharged tensions within the family and thus be of greater help to the child. Many may realize the difficulty of this approach, not only in the matter of time, but also in terms of the temptation to manipulate and guide the family in some authoritarian manner.

There are many other problems occurring in the everyday practice of medicine which could be discussed and perhaps need to be discussed. It is possible to refer to them only briefly at this point. There is the problem of preparing a parent and child for hospitalization, for an operative procedure or for an acute or chronic illness; the problem of the management of the chronically ill child and of helping him and his parents make an adjustment which will minimize the emotional disturbance; the problem of the children, and particularly the parents of the children, who are physically or mentally handicapped, the spastic child, the mentally retarded child; the problem of residual paralysis following poliomyelitis; that of the child with rheumatic heart disease, and many other similar problems. In all these instances the one therapeutic principle that needs emphasis is that the physician can be most helpful to the child by dealing with the parent or parents. Through empathy, listening and a noncritical attitude, he can to some extent help to drain off the overwhelming anxieties of the parents, relieve them of their sense of failure, inadequacy and guilt and in some measure reestablish the emotional equanimity which is the essential basis for improved intrafamilial relationships.

Parnassus and First Avenues (22).

SIMULTANEOUS NONFATAL SYSTEMIC HISTOPLASMOSIS IN TWO COUSINS

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UP UNTIL 1946 only 75 cases of systemic histoplasmosis had been reported in the literature and the impression obtained was that this disease was uniformly fatal.[1] Subsequent studies initiated by Christie and Peterson [2] and Palmer [3] demonstrated the relation of histoplasmin skin sensitivity to pulmonary calcification in tuberculin-negative persons. The actual infection leading to this state of histoplasmin sensitivity and pulmonary calcification has seldom been observed. In only 5 cases [4] has the infection been proved in patients who were ill with the disease and who subsequently recovered. Such cases offer strong support toward bridging the gap between the concept of uniform fatality on one hand and the benign subclinical forms on the other. The following 2 cases represent further instances of nonfatal systemic histoplasmosis with apparent recovery.

From the Department of Pediatrics, Ohio State University College of Medicine, the Children's Hospital, Columbus, Ohio, and the Department of Bacteriology, Army Medical Department Research and Graduate School, Washington, D. C.

1. Parsons, R. J., and Zarafonetis, C. J. D.: Histoplasmosis in Man, Arch. Int. Med. **75**:1 (Jan.) 1945.

2. Christie, A., and Peterson, J. C.: Histoplasmin Sensitivity, J. Pediat. **29**:417 (Oct.) 1946.

3. Palmer, C. E.: Geographic Difference in Sensitivity to Histoplasmin Among Student Nurses, Pub. Health Rep. **61**:474 (April 5) 1946.

4. (*a*) Bunnell, I. L., and Furcolow, M. L.: A Report on Ten Proved Cases of Histoplasmosis, Pub. Health Rep. **63**:299 (March 5) 1948. (*b*) Blumberg, R. W.; Ruchman, I., and Johansmann, R. J.: Generalized Non-Fatal Histoplasmosis in an Infant, Pediatrics **3**:296 (March) 1949. (*c*) Kunstadter, R. H.; Whitcomb, F. C., and Milzer, A.: Primary Histoplasmosis with Recovery of Histoplasma Capsulatum from the Blood and Bronchial Secretions, J. Lab. & Clin. Med. **34**:1290 (Sept.) 1949.

REPORT OF CASES

CASE 1.—The details of this case, that of J. H., an 8 year old white boy, were previously reported by Friedman, Brown and Turner.[5] Briefly, this boy had been in apparent good health until two months before his admission to the hospital, when he had an illness characterized by a week of irritability followed by a week of anorexia, fever, listlessness, headache and abdominal cramps after ingestion of food or liquid (fig. 1). A second identical attack occurred one month before his admission. A third similar attack had its onset eight days before his admission to the Children's Hospital, Columbus, Ohio. Examination revealed a well developed, well nourished boy who was listless and lethargic and complained of frontal headache. His temperature was 102.4 F., his pulse rate 100 and his respirations 24. There was generalized shotty, nontender adenopathy. Examination of the chest

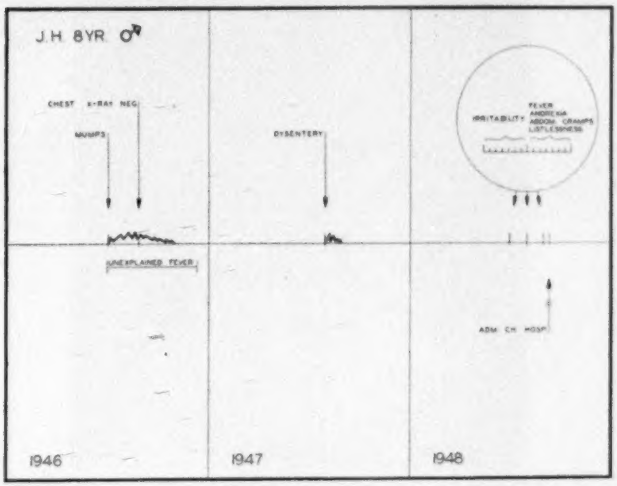

Fig. 1 (case 1).—Chart showing past history and data on present illness of J. H.

revealed a small area on the right posteriorly where there were depressed breath sounds but no rales. The edge of the spleen was tender and barely palpable. His blood contained 13.1 Gm. of hemoglobin per hundred cubic centimeters and 9,750 white blood cells per cubic millimeter, of which 60 per cent were neutrophils and 5 per cent were monocytes. A roentgenogram of the chest showed widely dispersed mottled, streaky infiltration throughout both pulmonary fields, denser in the bases and hilar regions and fading off toward the periphery (fig. 2). There was a knobby density in both hilar regions and a small amount of fluid was present in the base of the right lung. Intradermal tests with weak and strong tuberculin (purified protein derivative) gave negative reactions, but an intradermal test with histo-

5. Friedman, V.; Brown, J. E., Jr., and Turner, E. V.: A Case of Proven Systemic Histoplasmosis with Apparent Recovery, Ohio State M. J. **46**:44 (Jan.) 1950.

plasmin (1:1,000 dilution) resulted in a strongly positive reaction. The boy had a spiking fever (fig. 3) and became increasingly dyspneic. Although the presumptive diagnosis at this time was histoplasmosis, the boy was treated with penicillin and streptomycin because the possibility of bacterial pneumonia could not be eliminated. With histoplasmosis in mind, serum drawn on the eleventh day in the hospital was studied for the presence of specific antibodies by the complement fixation and collodion agglutination tests of Saslaw and Campbell.[6] The resultant complement fixation and agglutination titers of 1:1,280 and 1:320, respectively, presented strong evidence that the patient had active histoplasmosis. A definite diagnosis was made when Histoplasma capsulatum was isolated on the sixteenth day from blood obtained on his admission to the hospital. Another blood culture

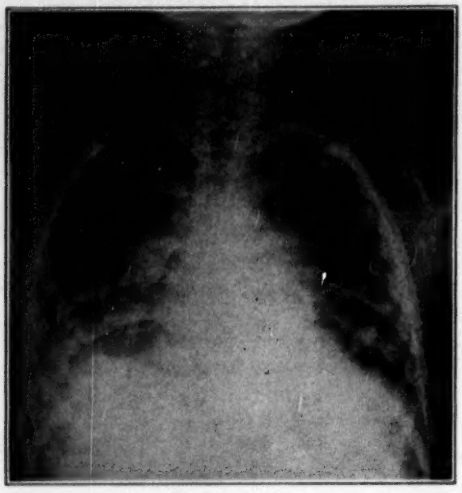

Fig. 2 (case 1).—Roentgenogram of the chest of J. H. taken on the fourth day (Aug. 17, 1948) of his first hospital admission.

6. (*a*) Saslaw, S., and Campbell, C. C.: The Use of Yeast Phase Antigens in a Complement Fixation Test for Histoplasmosis: I. Preliminary Results with Rabbit Sera, J. Lab. & Clin. Med. **33**:811 (July) 1948. (*b*) Campbell, C. C., and Saslaw, S.: The Use of Yeast Phase Antigens in a Complement Fixation Test for Histoplasmosis: II. Results with Ground Antigens, ibid. **33**:1207 (Oct.) 1948. (*c*) Saslaw, S., and Campbell, C. C.: A Method for Demonstrating Antibodies in Rabbit Sera Against Histoplasmin by the Collodion Agglutination Technic, Proc. Soc. Exper. Biol. & Med. **68**:559 (July-Aug.) 1948. (*d*) Campbell, C. C., and Saslaw, S.: Use of Yeast Phase Antigens in a Complement Fixation Test for Histoplasmosis: III. Preliminary Results with Human Sera, Pub. Health Rep. **64**:551 (May 6) 1949. (*e*) Saslaw, S., and Campbell, C. C.: A Collodion Agglutination Test for Histoplasmosis, ibid. **64**:424 (April 1) 1949.

taken on the eleventh day in the hospital was examined at the mycology laboratory of the Army Medical Department Research and Graduate School, at Washington, D. C., and was also positive for the Histoplasma organism.

By the end of two weeks the boy's fever had subsided and he felt much better. He was discharged, to be treated by continued rest in bed at home. He gained 4 pounds (1.8 Kg.) during the next two weeks, but he was then readmitted because of a recurrence of fever (fig. 4). Examination at this time revealed a state of general improvement. The spleen was hard, nontender and palpable 2 fingerbreadths below the left costal margin. His white blood cell count at this time was 7,600 and his hemoglobin concentration was 11.3 Gm. per hundred cubic centimeters. During this admission blood, stool and an inguinal lymph node were cultured for fungi but no organisms were isolated. Microscopic sections of the lymph node revealed focal granulomatous areas which contained organisms morphologically

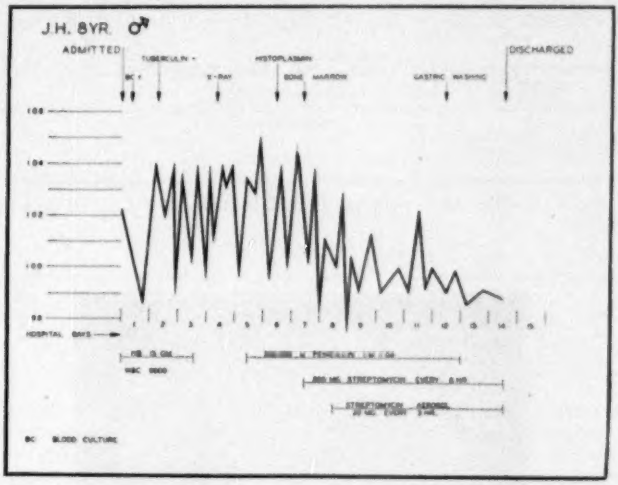

Fig. 3 (case 1).—Chart showing course in the hospital of J. H. on his first admission.

identical with H. capsulatum. By the time the child was discharged on the twelfth day from the hospital, the epitrochlear nodes were no longer palpable and other lymph nodes had decreased in size. The size of the spleen did not change. His temperature had again returned to normal and his appetite had improved. Roentgenographic examinations of the chest one, two and three months (fig. 5) after his discharge showed a clearing of the patchy infiltration in the periphery of the lung, and in the most recent of these films calcification had become evident in the left hilar nodes. The patient has moved away from Columbus, Ohio, and further roentgenologic and serologic examinations have been impractical. The boy is reported, however, to be in good health seventeen months after his first admission to the hospital and to be attending school. With clinical recovery there was a concurrent decrease in the antibody titer in this child. The complement fixation

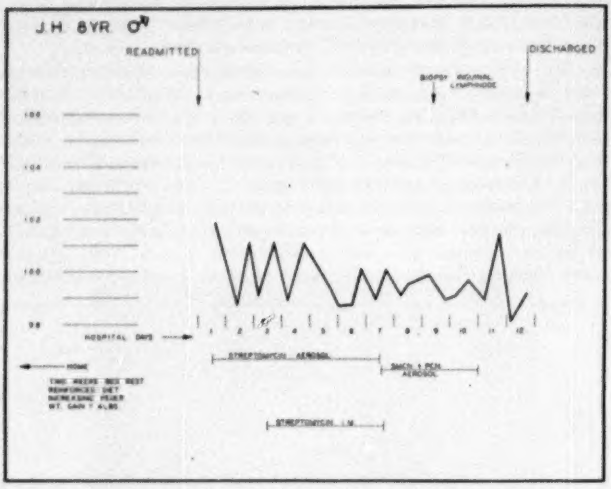

Fig. 4 (case 1).—Chart showing course in the hospital of J. H. on his second admission.

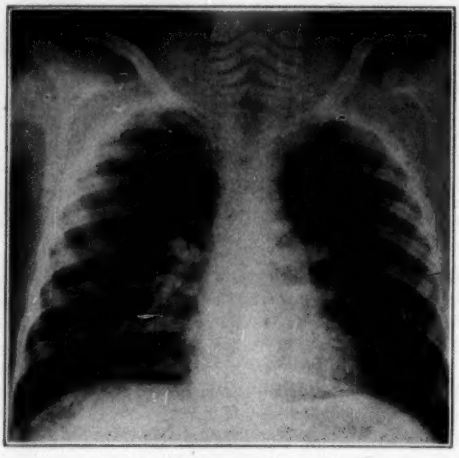

Fig. 5 (case 1).—Roentgenogram of the chest of J. H. taken four months after his first admission to the hospital (Dec. 20, 1948).

titer on serum drawn four months after the initial test was 1:40, as compared with 1:1,280. The collodion agglutination reaction was negative, in contrast to the earlier titer of 1:320. The serologic results are listed in the table. The transient nature of the antibody response in histoplasmosis has been described elsewhere.[7]

CASE 2.—This 5½ year old white boy, R. R., who was the cousin and constant companion of J. H. (case 1) was admitted to Children's Hospital for the first time four days after the first admission of his cousin. He had had a prolonged chest cold which had lasted through the previous winter. It was characterized by a hard, croupy cough and was diagnosed as chronic bronchitis. Following this, he was perfectly well until eight days prior to his admission when a sore throat developed which lasted a day and a half (fig. 6). He had had headache, anorexia and an elevation in temperature to 104 and 105 F. for six days. There had been an occasional complaint of abdominal pain following the ingestion of food or drink for four days. Physical examination on his entry revealed a well developed, well nourished boy resting quietly in bed. The child was lethargic and listless but had

Titers of Complement Fixation and Collodion Agglutination Tests for Histoplasmosis in Cases 1 and 2

	Date	Complement Fixation Titer	Collodion Agglutination Titer
Case 1 (J. H.)	8/24/48	1,280	160
	9/ 5/48	640	...
	9/25/48	320	80
	10/29/48	40	80
	12/21/48	40	<5
Case 2 (R. R.)	8/24/48	20	20
	10/20/48	160	80
	2/20/49	10	5
	9/10/49	10	<5

no complaints. His color was excellent; his skin was hot and moist, and there was no eruption. The anterior and posterior cervical, axillary, epitrochlear and inguinal lymph nodes were all palpable and somewhat enlarged, but they were not tender. The mucous membrane of the pharynx was inflamed. The chest was symmetric, of equal expansion and resonant to percussion. On auscultation the breath sounds were somewhat tubular, and scattered, fine, sticky crepitations were heard on both sides posteriorly. The edge of the liver was palpable, firm and nontender. The spleen was palpable 2 fingerbreadths below the left costal margin with a firm edge and was nontender. The reflexes were hyperactive throughout and there was an unsustained patellar clonus bilaterally. The temperature was 100.8 F., the pulse rate 100 and the respirations 20.

Urinalysis on his admission gave essentially normal results. His blood contained 13.5 Gm. hemoglobin and 9,000 white blood cells, of which 42 per cent were neutrophils and 2 per cent were monocytes. Two days later his leukocyte count was 7,900. A blood culture taken on his admission was contaminated. A tuberculin patch test gave a negative reaction but the reaction to an intradermal skin test with histoplasmin (1:1,000) was positive. A roentgenogram of the chest on the

7. (*a*) Campbell and Saslaw.[6d] (*b*) Saslaw, S., and Campbell, C. C.: Serologic Studies in Histoplasmosis, to be published.

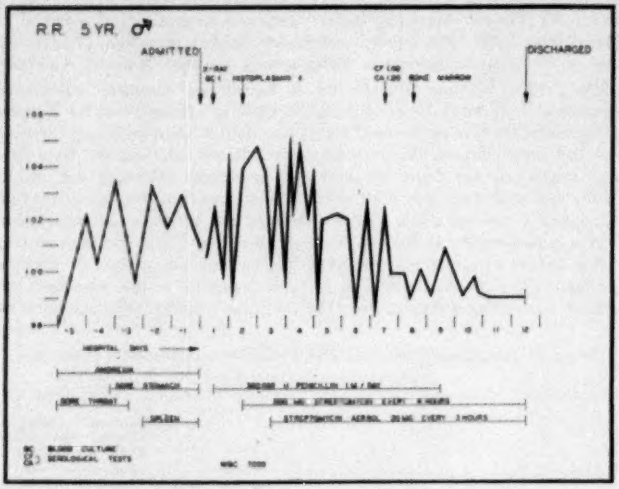

Fig. 6 (case 2).—Chart showing history of present illness and course in the hospital of R. R.

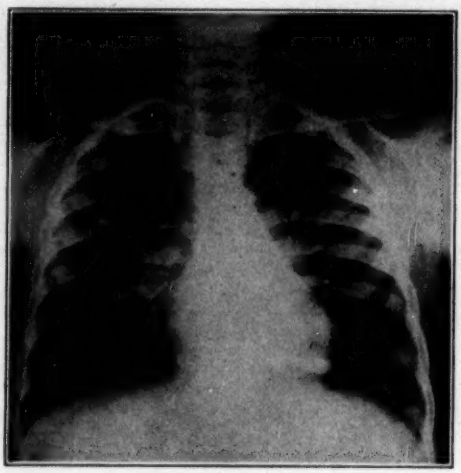

Fig. 7 (case 2).—Roentgenogram of the chest of R. R. taken on his admission to the hospital (Aug. 18, 1948).

day of his admission showed knobby hilar densities bilaterally and infiltration along both cardiac borders (fig. 7). The periphery was clear. There was slight widening of the upper mediastinal shadow adjacent to the heart. There was fluid or thickening of the pleura in the right interlobar septum. A roentgenogram of the chest of the patient's mother taken at this time showed a few calcified shadows in the left hilar region and the left pole of the right hilus. Her histoplasmin skin test gave a negative reaction. Roentgenographic examination of the father's chest showed patchy areas of calcification in the hilar regions bilaterally. His cutaneous reaction to histoplasmin was positive. The patient's 4 year old sister had both a normal chest roentgenogram and a positive reaction to the histoplasmin skin test.

Serum drawn on the sixth day in the hospital showed complement-fixing antibodies in a titer of 1:40 and a collodion agglutination titer of 1:40. In the meantime, with the suggestive clinical and serologic picture, an intensive search

Fig. 8 (case 2).—Roentgenogram of the chest of R. R. taken one year after his admission to the hospital.

was made for H. capsulatum with the resultant successful recovery of the organism at the Army Medical Department Research and Graduate School from blood drawn on the sixth hospital day. This organism took five weeks to grow out on laboratory mediums.

During the first week in the hospital the patient had one to two daily spikes in temperature to 104 or 105 F. This boy, like his cousin, was treated with penicillin and streptomycin because the possibility of bacterial pulmonary infection could not be excluded. On the sixth day in the hospital the fever began to decrease and in the second week his temperature returned to normal by lysis. By the thirteenth day in the hospital roentgenographic examination of his chest showed considerable clearing of the infiltration around the hilar regions. The knobby densities in the hilar regions remained unchanged.

With the fall in temperature the child showed daily improvement in both disposition and appetite. He had no cough or dyspnea. Lymphadenopathy and splenomegaly persisted. He was discharged on the thirteenth day from the hospital. Serologic studies five weeks after his admission showed a 1:160 complement fixation titer and 1:80 collodion agglutination titer. Five and a half months after his admission his titers were 1:10 and negative, respectively. One year after the initial studies both tests gave negative results. The boy has remained in excellent health. One year after his admission his roentgenograms still showed a moderate knobby enlargement of the hilar glands but no evidence of calcification (fig. 8). Seventeen months after his admission a few small areas of beginning calcification were visible in the hilar regions. The table summarizes the serologic findings in both cases.

COMMENT

The relation of histoplasmin skin sensitivity to pulmonary calcification in tuberculin-negative persons has already been mentioned. Similar observations have been repeated on a large scale and found to be true for a large area of the Middle West.[8] Our 2 cases represent instances of proved Histoplasma infection in cousins living near Columbus, Ohio, in a rural area considered endemic for histoplasmosis. Prior and Allen [9] showed recently that in the area in which these boys reside 62 per cent of young adults have positive reactions to histoplasmin skin tests. Although J. H. was in various sections of the country during the war, he had lived constantly in this vicinity since 1944. A roentgenographic examination of his chest in 1946 showed no pulmonary abnormalities; therefore, presumably, these boys' infections started since 1946. It is interesting to note that both became sick at about the same time.

In a systematic search for the infection which gave rise to positive cutaneous reactions to histoplasmin, Furcolow, Mantz and Lewis [10] examined the chest roentgenograms of 16,000 school children in Kansas City, Mo., and discovered 72 asymptomatic children who had persistent (of more than two months' duration) pulmonary lesions associated with positive reactions to histoplasmin skin tests and negative reactions to tuberculin tests. The fungus could not be isolated from these children. In their geographic area such persistent pulmonary infiltrations were associated oftener with histoplasmin than with tuberculin sensitivity.

8. Christie and Peterson.[2] Palmer.[3] Smith, C. E.; Saito, M. T.; Beard, R. R.; Rosenberger, H. G., and Whiting, E. G.: Histoplasmin Sensitivity and Coccidioidal Infection, Am. J. Pub. Health **39**:722 (June) 1949.

9. Prior, J. A., and Allen, M. F.: Geographic Distribution of Histoplasmin and Tuberculin Reactors Among Ohio State University Freshman and Student Nurses Training in Columbus, Ohio, Hospitals, Pub. Health Rep. **62**:1608 (Nov. 7) 1947.

10. Furcolow, M. L.; Mantz, H. L., and Lewis, L.: The Roentgenographic Appearance of Persistent Pulmonary Infiltrates Associated with Sensitivity to Histoplasmin, Pub. Health Rep. **62**:1711 (Dec. 5) 1947.

Sontag and Allen [11] studied serial chest roentgenograms of 170 normal Ohio infants for a number of years. Later they applied histoplasmin tests to the entire group and observed that most of the 103 instances of pulmonary calcification which had been noted were associated with histoplasmin sensitivity. The initial soft tissue lesion frequently appeared before the age of 1 year and in the majority before 4 years. Although some lesions calcified in a few months, others showed a lag of two years or more. The process seemed to be a progressive one, new soft tissue lesions appearing and going on to calcification over a period of six or more years. This suggests that the infection may remain active even though subclinical for a long period.

Kunstadter, Whitcomb and Milzer [4c] reported a case of primary histoplasmosis in a 12 year old boy with clinical signs of atypical pneumonia. The course of the infection was followed from the onset through the stage of pulmonary infiltration to healing with beginning pulmonary calcification. H. capsulatum was isolated from the blood and bronchial secretions during the acute stage. Bunnell and Furcolow [4a] reported 10 proved cases of histoplasmosis in residents of the Kansas City, Mo., area. Three of the 10 persons recovered. One of those who recovered, a 13 year old boy attending school, exhibited only mild illness (malaise and headache for three months) but was found to have miliary lesions in both pulmonary fields, with enlargement of hilar nodes noted on roentgenologic examination. The other 2 who recovered were infants studied because of their severe symptoms (fever, hepatomegaly, splenomegaly, anemia and leukopenia). Blumberg, Ruchman and Johannsmann [4b] also reported the case of an infant who was severely ill (fever, hepatomegaly, splenomegaly, anemia and leukopenia) and who recovered.

The subject of fatal histoplasmosis was reviewed by Parsons and Zarafonetis [1] and by Iams and Keith,[12] who refer especially to the disease in infants. The major clinical findings in the series of Iams and Keith were, in order of frequency: fever, loss of weight, hypochromic normocytic anemia, splenomegaly, hepatomegaly, leukopenia and lymphadenopathy. In their patients seen at postmortem examination the fungus was reported to involve, in order of frequency: lungs, lymph nodes, liver, spleen and gastrointestinal tract. In addition, they mentioned the occasional occurrence of dermatitis and infection of the upper respiratory tract, as well as infection in the bone marrow, adrenal glands, thymus, skin, pancreas, myocardium, kidneys and brain. The clinical features exhibited by our 2 children showed no significant difference from those

11. Sontag, L. W., and Allen, J. E.: Lung Calcifications and Histoplasmin-Tuberculin Skin Sensitivity, J. Pediat. **30**:657 (June) 1947.

12. Iams, A. M., and Keith, H. M.: Histoplasmosis in Infancy, J. Pediat. **30**:123 (Feb.) 1947.

previously reported in fatal cases. The progressive clearing of the pulmonary infiltration and its replacement by small calcified lesions in J. H. are in striking agreement with the observations of Furcolow and his associates,[10] Sontag and Allen[11] and Kunstadter and his co-workers.[12]

Histoplasma infections in children are characterized usually by fever, lymphadenopathy, hepatomegaly, splenomegaly and massive pulmonary infiltrations, with minor symptoms pointing to the pulmonary involvement. It is apparent that the symptoms and physical findings alone might indicate such disease conditions as leukemia, brucellosis, infectious mononucleosis, atypical pneumonia or tuberculosis. Immunologic tests indicate paths of further investigation in such cases. A positive intradermal reaction may suggest past or present infection with H. capsulatum. In this respect the histoplasmin test is comparable to that with tuberculin or "brucellergen." During overwhelming infections with Histoplasma the cutaneous reaction may be negative. On the other hand, recent observations indicate that the humoral antibodies[7] are significantly elevated only during the acute stage of the disease and that as the disease progresses either toward recovery or toward death the antibody titers diminish. In patients with chronic Histoplasma infections or in patients with healed infections the antibody titer is usually insignificant. The preliminary results of Saslaw and Campbell[7b] suggested that a positive complement fixation reaction in a dilution of 1:40 or more or a 4 plus collodion agglutination reaction in a dilution of 1:10 or greater in their tests is presumptive evidence of active infection. The histologic picture of the infection in lymph nodes and occasionally in the bone marrow may permit a definite diagnosis by biopsy. Final proof, however, comes from the isolation of the organism from the patient by culture. Blood, bone marrow, sputum, gastric washings or biopsy material may be cultured.

It is interesting to note that in the case of J. H. the original culture was obtained with the use of routine blood culture mediums. Ordinarily, in our laboratory we use tryptose phosphate broth with the addition of 0.1 per cent agar. On review of the circumstances surrounding the original isolation, it was noted that the particular batch of medium into which this boy's blood was inoculated had been made up in error, so that it contained probably about 0.4 per cent agar. Salvin[13] noted that Histoplasma grows much more profusely in mediums containing small amounts of agar. The original growth was noted after sixteen days of incubation at 37 C. (98.6 F.) under partial tension of carbon dioxide.

13. Salvin, S. B.: Cultural Studies on the Yeastlike Phase of Histoplasma Capsulatum Darling, J. Bact. **54**:655 (Nov.) 1947.

At a later date blood was taken on both of these patients and sent to the Army Medical Department Research and Graduate School where the workers, using their technic, accomplished isolations for both patients.

At the Army Medical School isolation of Histoplasma was accomplished by inoculation of the specimen into veal infusion broth with 1 per cent dextrose to which was added 40 units of streptomycin and 20 units of penicillin each per cubic centimeter of medium. The p_H of this broth was adjusted to about 7.4. Such blood cultures were made in duplicate, one flask being incubated at room temperature, the other at 37 C. for at least three weeks. Subcultures were made to Francis' cystine agar, regardless of whether growth was apparent or not. These subcultures were incubated at 37 C. for at least two additional weeks. Duplicate transfers were incubated at room temperature for the production of characteristic "tuberculate" chlamydospores.

	TYPE	AUTHORS	NO. OF CASES	SKIN TEST	ANTIBODIES	CULTURE	CHEST X-RAY	PULMONARY CALCIFICATION	HEPATO-SPLENOMEGALY
1	FATAL SYSTEMIC	IAMS	RARE	+	?	+	INFILTRATION	–	+
		KEITH	FEW	–			+ OR –		
2	NON FATAL SYSTEMIC	BUNNELL	FEW	+	+	+	INFILTRATION	–	+
		BLUMBERG					+ OR –	+	
3	NON FATAL SYMPTOMATIC PULMONARY	RUBSTADTER ET AL.	FEW	+	?	+	INFILTRATION	–	–
		BUNNELL					+	+	
4	ASYMPTOMATIC PULMONARY	SORTAG & ALLEN	MANY	+	+	–	INFILTRATION	–	–
		TURCOLOW					+	+	
5	HEALED	CHRISTIE	MANY	+	+	–	–	+ OR –	–
		PALMER							

Fig. 9.—Spectrum of types of involvement by Histoplasma in children as described by various authors.

It is apparent from the foregoing discussion that Histoplasma infections in children display a spectrum of severity of involvement (fig. 9). There are a few persons living in endemic areas who acquire a generalized infection with the fungus and die. During the infection the organism appears in the blood and the bone marrow; the liver, spleen and lymph nodes are enlarged, and there is often pulmonary infiltration. Usually, the patient dies before the pulmonary infiltration clears and is replaced by calcification. These patients have a positive cutaneous reaction to histoplasmin shortly after the onset of their infection, but this sometimes disappears at the height of the disease, presumably because of an anergic response of the patient to overwhelming infection. Humoral antibodies also appear shortly after the onset but may later diminish in titer and be absent at the time of death. This type of involvement was well reviewed by Iams and Keith.[12]

A few other persons acquire similar infections but recover spontaneously. In these patients the organism can also be recovered from blood or bone marrow and perhaps from bronchial secretions. Pulmonary infiltration is usually present, and, after this has cleared, calcium is deposited in the parenchyma of the lung or in the hilar nodes. The cutaneous reaction in these persons is, as far as we know, always positive. The humoral antibodies rise to their height within a few months after the onset of the infection and later diminish in titer and may even become absent. Our own cases, that of Blumberg and his associates [4b] and those of the 2 infants of Bunnell and Furcolow [4a] represent this degree of severity.

A few other persons, usually older children, show symptoms of pneumonitis but do not have the severe systemic involvement characteristic of infants. The organisms may be cultured from the blood and also from the pulmonary secretions. The pulmonary infiltration resolves slowly and is in time replaced by calcification. The cutaneous reaction is positive, and the humoral antibody response is presumably similar to that stated for the foregoing type. This type is illustrated by the cases of Kunstadter and his co-workers [4c] and the first case mentioned by Bunnell and Furcolow.[4a]

A large number of persons living in endemic areas probably acquire asymptomatic pulmonary infections which resolve with evidences of calcification. These persons have positive cutaneous reactions and their humoral antibodies eventually diminish to low titers. Such cases are illustrated by those reported by Sontag and Allen [11] and by Furcolow, Mantz and Lewis.[10]

Whether all persons discovered to have positive reactions to histoplasmin tests and pulmonary calcification represent instances of healed infections of the foregoing type is not clear. Some histoplasmin-positive persons show no calcium deposits in their lungs, a fact which leads to the speculation that sometimes the positive cutaneous reaction may reflect healed systemic lesions rather than healed pulmonary lesions.

The therapy for our 2 patients consisted essentially of rest in bed and a diet similar to that used for patients with tuberculosis. It is our considered opinion that none of the drugs used, the streptomycin, the sulfadiazine or the penicillin, contributed significantly to their recovery. In fact, in vitro studies by Campbell and Saslaw [14] on the enhancement of the growth of certain pathogenic fungi by streptomycin suggest caution in the use of this antibiotic in the treatment of clinical Histoplasma

14. Campbell, C. C., and Saslaw, S.: Enhancement of the Growth of Certain Pathogenic Fungi by Streptomycin, Proc. Soc. Exper. Biol. & Med. **70**:562 (March) 1949.

infections. It is likely that within the next few years there will be brought forth chemotherapeutic agents active against systemic fungus infections. We wish to emphasize that these 2 patients recovered without the benefit of any specific fungicidal agents. In the future, recoveries reported to be due to the effect of such agents should be considered in the light of possible spontaneous remissions of the disease.

It is our feeling that with the greater use of precise diagnostic methods, especially the cultural isolation of the organism from patients, more and more observations similar to ours will be made. The recently developed serologic tests will probably serve as a diagnostic tool to select patients for such cultural studies and to increase the number of cases correctly diagnosed.

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Miss Charlotte C. Campbell, of the Army Medical Department Research and Graduate School, identified the organisms and assisted in the performance of the serologic tests.

THROMBOPENIC PURPURA

Report of Four Cases in One Family

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AND
MARTIN H. SMITH, M.D.
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HEREDITARY thrombopenic purpura has been the subject of considerable controversy. The standard textbooks mention the possibility of such a diathesis without definitely accepting its existence. Quick [1] stated:

> Although the suggestion has been made that there may be an hereditary or constitutional disposition to the disease (primary thrombocytopenic purpura), a careful study of the literature does not bear this out.

However, Hess [2] in 1916 reported 3 cases of purpura from different families who showed low thrombocyte counts and gave a history of purpura in other members of the family. Unfortunately, he gave no laboratory data on the other members of the families.

Glanzmann [3] in 1918 reviewed the entire subject of purpura. From his clinical observations and experiments he concluded that there is a hereditary hemorrhagic diathesis which affects both females and males, in contrast to hemophilia. In 1932, Witts [4] reported on three families who showed a hereditary hemorrhagic diathesis. In one family four generations could be traced, and the mother in the second generation apparently had latent thrombopenia, with the history of her brother and sister showing signs of the disease. Three of her children had purpura and low thrombocyte counts were demonstrated in them. His second family had 3 children who showed purpura and low thrombocyte counts but persons in previous generations displayed no signs of the disease. One of these 3 children died following splenectomy and the other 2 had no serious bleeding tendency. Members of his third family had hemorrhagic diatheses but showed no abnormal blood findings. Witts listed three forms of hereditary hemorrhagic diatheses: (*a*) hemo-

1. Quick, A. J.: The Hemorrhagic Diseases and the Physiology of Hemostasis, Springfield, Ill., Charles C Thomas, Publisher, 1942, p. 133.

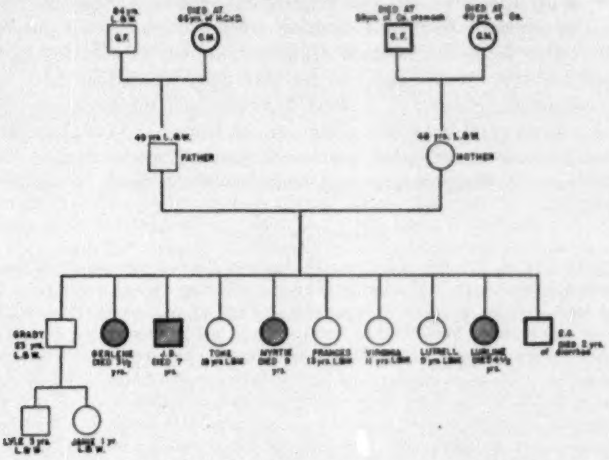
2. Hess, A. F.: The Blood and the Blood Vessels in Hemophilia and Other Hemorrhagic Diseases, Arch. Int. Med. **17**:203 (Feb.) 1916.

3. Glanzmann, E.: Hereditäre hämorrhagische Thrombasthenie, Jahrb. f. Kinderh. **88**:1 and 113, 1918.

4. Witts, L. J.: The Hereditary Haemorrhagic Diathesis, Guy's Hosp. Rep. **82**:465, 1932.

philia, (*b*) hereditary hemorrhagic telangiectasis and (*c*) simple hereditary hemorrhagic diathesis. He made no differentiation in the third group as to whether or not thrombopenia is manifested.

A number of reports have appeared in the literature of thrombopenic purpura occurring in the newborn infant of a mother with evidence of the disease.[5] Most of these cases were described from the obstetric point of view and the reports gave only minimal information about the baby. Sanford and his associates [6] reported a similar case in 1936 and review the literature up to that time. They found 9 previously reported cases that they judged could be authenticated. In 1945, Morrison and Samwick [7] reported a new case and set up the criteria for



Pedigree of family with familial thrombopenic purpura in 4 members. Shaded circles and squares represent the 4 children reported on. *L. & W.* indicates member was living and well at time of study. *Ca.* indicates cancer and *H. C. V. D.* hypertensive cardiovascular disease.

5. Rushmore, S.: Purpura Complicating Pregnancy, Am. J. Obst. & Gynec. **10**:553, 1925. Leibling, P.: Purpura Hemorrhagica Complicating Pregnancy, ibid. **11**:847, 1926. Siegler, S. L.: Purpura Hemorrhagica Complicating Pregnancy, M. Rec. **139**:189, 1934. Greenwald, H. M., and Sherman, I.: Congenital Essential Thrombocytopenia, Am. J. Dis. Child. **38**:1245 (Dec.) 1929. Davidson, L. T.: Congenital Thrombopenia, ibid. **54**:1324 (Dec.) 1937. Patterson, W. B.: Thrombocytopenia Purpura in Pregnancy and in the Newborn, J. A. M. A. **130**: 700 (March 16) 1946.

6. Sanford, H. N.; Leslie, E. I., and Crane, M. M.: Congenital Thrombocytopenia, Am. J. Dis. Child. **51**:1114 (May) 1936.

7. Morrison, M., and Samwick, A. A.: Congenital Essential Thrombopenic Purpura, Am. J. Dis. Child. **70**:115 (Aug.) 1945.

diagnosis of congenital essential thrombopenic purpura. On the basis of their criteria they discarded a number of the previously reported cases as insufficiently proved or as deviates from the expected picture. One case [8] has been reported of thrombopenic purpura in an infant without a similar disease in the mother; however, bleeding and clot retraction times were not prolonged in this instance. Imerslund [9] reported hemorrhagic diatheses in three families with male and female members affected. The blood findings were normal except for a prolonged bleeding time. These disorders seem to be essentially the same as those others have reported and called pseudohemophilia.

The cases herein presented are all of siblings in the same family. The family has now been followed thirteen years. During this time 3 of the children have died showing definite thrombopenic purpura, and 1 other died with identical symptoms without ever having had a hospital study. No persons in the preceding generations have had any symptoms or signs of a blood dyscrasia, and the laboratory data on the mother and father are within normal limits. So far as possible, toxins, infections and other conceivable causes for the disease were ruled out. A diagrammatic representation of the family is given in the figure.

REPORT OF CASES

Case 1 (J. B. B.).—This 6½ year old boy was the first member of the family admitted to the hospital. The family history at this time showed that a sister had died when 3½ years old with hemorrhages from all mucous membranes. The patient was bleeding from his nose, gums, kidneys and intestine at the time of his admission. He was said to have always bruised easily and for three years he had had severe episodes of epistaxis. For two years, at intervals of two to three months, he had bled from his genitourinary and gastrointestinal tracts. The results of physical examination of all systems were not remarkable except for the presence of bruises over the entire body. The liver and spleen were not palpable.

Laboratory data on his admission showed an erythrocyte count of 1,440,000, a hemoglobin concentration of 33 per cent and 3,700 leukocytes, with 45 per cent neutrophils, 48 per cent lymphocytes, 2 per cent juvenile forms and 5 per cent band forms. The thrombocyte count was 30,000; the bleeding time was five and a half minutes and the coagulation time six minutes. The blood Wassermann reaction was negative. His urine on admission showed a few red blood cells per high power field. Roentgenograms of the sinuses and long bones were normal. The fragility test showed normal hemolysis.

The patient continued to bleed at intervals for two weeks. Two transfusions totaling 470 cc. brought his blood counts out of the danger level. Repeated thrombocyte counts never showed a higher content than 90,000 per cubic millimeter. The leukocyte counts never exceeded 6,700 cells and the differential count remained

8. Schefrin, A. E., and Schectman, A.: Congenital Thrombopenia, Am. J. Dis. Child. **70**:29 (July) 1945.

9. Imerslund, O.: Familial Haemorrhagic Diasthesis with Prolonged Bleeding-Time, Acta pædiat. **34**:315, 1947.

normal. He was discharged from the hospital one month after his admission. The child died six months later after massive hemorrhages from the gastrointestinal and genitourinary tracts. He was not returned to the hospital before his death.

CASE 2 (M. E. B.).—This girl was admitted to the hospital at the age of 9 years, seven years after the brother was admitted. She had had a normal, full term birth and previous illnesses had included only the usual childhood diseases. She had begun to bleed from the nose five months before her admission and continued to bleed at intervals from the nose and gums until she had an obvious anemia. Physical examination showed a weight of 56 pounds (25.4 Kg.). She was normally developed but obviously pale and poorly nourished. There was a blowing systolic murmur at the apex of the heart. Spleen and liver were not felt.

On her admission laboratory data showed a red blood cell count of 500,000, a hemoglobin concentration of 1.8 Gm. and a white blood cell count of 3,300, with 16 per cent neutrophils, 84 per cent lymphocytes and 4 per cent band forms. The thrombocyte count was 15,000 per cubic centimeter, and the reticulocyte count was 1.4 per cent. The bleeding time was five minutes and the clotting time six minutes. In the fragility test hemolysis began at 0.42 per cent sodium chloride and was complete at 0.36 per cent, which was identical with the control values. A roentgenogram of the chest showed the heart to be enlarged in all diameters. Roentgenograms of the long bones had a normal appearance. Repeated blood counts reflected only the improvements in red cell count and hemoglobin concentration due to transfusions or the decreases due to repeated bleeding episodes. Frequently repeated thrombocyte counts never showed a value above 45,000 per cubic millimeter. Studies of the bone marrow were made and it was found to be normal.

The patient had frequent transfusions but continued to bleed at intervals. No medications were of any help. The bleeding into the gastrointestinal tract finally became severe, and she died five months after her admission. Autopsy showed hemorrhages into all tissues and organs. The bone marrow appeared somewhat hyperplastic, but otherwise normal.

CASE 3 (L. B.).—The patient was 3½ years old at the time of her first admission to the hospital. She had begun to show bleeding gums one month earlier, and the day before her admission she began to bleed from her nose and vomited blood. The patient had always bruised easily. There was no history of ingestion of any possible toxin. Physical examination showed a drowsy, pale girl with numerous bruises over the entire body. The nose was oozing venous blood, and the gums were covered with blood. The heart was slightly enlarged and the rate was 148. There was a loud systolic murmur at the apex. The spleen and the liver could not be felt.

Laboratory data on her admission showed the hemoglobin concentration to be 3.5 Gm. and red blood cell count 1,360,000. The white blood cell count was 4,050, with 57 per cent lymphocytes, 43 per cent neutrophils, 1 per cent juvenile forms and 11 per cent band cells. The thrombocyte count was 30,000 and the reticulocyte count 0.1 per cent. The bleeding time was four minutes and the clotting time five minutes; the clot was not firm or retracted after twenty-four hours. Prothrombin time for the patient was twenty-one seconds and for the control twenty-three seconds. Hemolysis on fragility tests on two occasions was normal. Roentgenograms of the chest and long bones showed nothing unusual. Repeated urinalyses gave normal results, except that on occasions the urine was flooded with red blood cells.

Following her admission, repeated blood counts showed only a rise in hemoglobin concentration and red blood cell count due to transfusions or a fall resulting

from recurrence of bleeding. The patient's hemoglobin content was brought up to a normal level on several occasions only to show a fall when bleeding recurred. Throughout her stays in the hospital, the white blood cell count remained below 12,000 and the differential picture was normal. Study of the sternal marrow showed striking deficiency of the megakaryocytes, with degenerating nuclei in some sections.

The patient was given calcium, a vitamin K preparation and moccasin venom with no effect on the thrombocyte count or the bleeding. One month after the onset of the bleeding splenectomy was done. Before the operation the thrombocyte count was 55,000; immediately after the operation it was 65,000; twenty-five minutes later it was 80,000, and six and a half hours after operation it was 120,000. The thrombocyte count soon fell back to 20,000, however, and the patient's symptoms continued unchanged.

During the ten months following the onset of bleeding, the patient received a total of 14,510 cc. of whole blood by direct or indirect transfusions. Each transfusion slowed the bleeding temporarily, but it soon returned. When it was apparent that the patient's condition was not going to improve permanently, the transfusions were stopped. The bleeding continued from the nose, gums and gastrointestinal and genitourinary tracts. The patient died ten months after the onset of the bleeding.

Autopsy showed generalized purpura, anemia, subdural hemorrhage and interstitial pneumonia. There were areas of hemorrhage in the gastrointestinal tract, kidneys and brain. The bone marrow showed hyperplastic cells and numerous eosinophils, but no megakaryocytes could be identified.

COMMENT

The family was surveyed three years ago in an attempt to detect the latent presence of this disease in any other members. At that time examinations of all the family, except 1 sibling (T.B.), gave normal results; one of her thrombocyte counts recorded was 60,000 cells per cubic millimeter. Recently, the family was surveyed again and the study then included three generations. All the surviving members showed normal blood counts, thrombocyte counts and bleeding, clotting and clot retraction times. All the family has been free clinically of any bleeding tendency except those whose deaths are reported.

We do not feel that these cases are similar to the numerous reported cases of congenital thrombopenic purpura in an infant born of a mother showing thrombopenia. This mother has never shown any clinical or laboratory evidence of the disease. All the children affected progressed three to seven years in life with no serious indication of the disease. Likewise, there are some discrepancies in these cases in regard to Morrison and Samwick's[7] criteria for the diagnosis of congenital thrombopenic purpura.

The usual classification of thrombopenic purpuras divides them into primary and secondary groups. Secondary purpura, due to infection, can be ruled out in all these children. No basis for thrombopenia due to a toxin or poison could be found in any of the patients. Numer-

ous bone marrow studies and autopsies on 2 of the children showed no marrow destruction or any other specific cause for the thrombopenia. Primary thrombopenic purpuras are usually divided into the congenital and the essential or idiopathic types. Dameshek and Miller [10] reported an increased number of megakaryocytes but decreased production of thrombocytes by the megakaryocytes in idiopathic thrombopenic purpura. The bone marrow studies on these patients at different stages of their disease were interpreted as showing normal or decreased numbers of megakaryocytes.

It is difficult to classify the disease of these patients in any of the usual groups of thrombopenia. The bone marrow picture presented by one (case 3) was that of an aplasia specifically affecting the megakaryocytes. Certainly it seems to be more than coincidental that 4 members of one family should be affected by this disease.

The situation seems similar to that in the families described by Hess [2] and Witts [4] which they called hereditary hemorrhagic diathesis. We think that the condition in our patients can be more specifically called familial thrombopenic purpura. In addition, the disorder in patients such as these who show familial thrombopenia should be considered a distinct entity, apart from the condition in those who do not present thrombopenia but show only a prolonged bleeding time.

SUMMARY

The case histories of 4 children in one family who died with hemorrhagic diatheses are reported. Three of these children were studied in the Henrietta Egleston Hospital for Children, Atlanta, Ga., and were shown to have thrombopenic purpura. Study of the other members of the family failed to reveal the latent presence of the disease in them. We believe that the disease in these patients could be classified as familial thrombopenic purpura.

33 Ponce de Leon Avenue, N. E.

10. Dameshek, W., and Miller, E. B.: The Megakaryocytes in Idiopathic Thrombocytopenic Purpura: A Form of Hypersplenism, Blood **1**:27, 1946.

URINARY EXCRETION OF GLUCURONIC AND SALICYLIC ACIDS IN NORMAL AND IN RHEUMATIC CHILDREN

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A STUDY of the excretion of glucuronic (also glycuronic) acid in the urine is generally connected with the study of the excretion of substances with a phenolic or alcoholic structure which are conjugated with glucuronic acid in the liver.

This study, however, was undertaken for the following reason. It is generally recognized that the pathologic manifestations of the primary lesion in rheumatic fever are found in the collagenous connective tissues of the body. The connective tissues have within them "mucoid" which contains glucuronic acid [1] and hyaluronic acid, a mucopolysaccharide composed of glucosamine and glucuronic acid in a proportion of 1:1.[2] It was, therefore, thought that children with rheumatic fever might manifest some specific disturbance of glucuronic acid metabolism which could be detected by examination of the urine with and without the administration of acetylsalicylic acid, a compound which in part becomes conjugated with glucuronic acid. If this disturbance did occur, its detection might be important in the early differential diagnosis of rheumatic fever.

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* La Rabida research fellow for 1947 to 1949, by a grant from the Morris Fishbein Jr. fellowship.

1. Meyer, K.: Mucoids and Glycoproteins, in Anson, M. L., and Edsall, J. T.: Advances in Protein Chemistry, New York, Academic Press, 1945, vol. 2, p. 249.

2. Meyer, K., and J. W. Palmer: On Glycoproteins: The Polysaccharides of Vitreous Humor and of Umbilical Cord, J. Biol. Chem. **114**:689, 1936. Meyer, K.; Hobby, G. L.; Chaffee, E., and Dawson, M.: Hydrolysis of Hyaluronic Acid by Bacterial Enzymes, J. Exper. Med. **71**:137, 1940. Meyer, K.: The Biological Significance of Hyaluronic Acid and Hyaluronidase, Physiol. Rev. **27**: 335, 1947. Meyer, K., and Ragan, C.: Hyaluronic Acid and the Rheumatic Disease, Mod. Concepts Cardiovas. Dis., vol. 17, no. 2, 1948.

URINARY EXCRETION OF GLUCURONIC ACID BY NORMAL AND BY RHEUMATIC CHILDREN

Experimental Method.—Chemical Method: The method of Dische[3] was used without modification, since glucuronic acid added to urine could be estimated quantitatively with an error of 1 per cent. It should be noted that the addition of acetylsalicylic acid to the urine did not modify the results obtained for the glucuronic acid content by Dische's method. The methods used for other tests employed in this study will be provided later.

TABLE 1.—*Data Obtained on the Twenty-Four Hour Urine Specimens of Normal Children*

Name	Age, Years	Sex	Total Output, Cc. in 24 Hr.	Morning Fasting Urine, Glucuronides, Mg./100 Cc.	Total 24 Hr. Excretion of Glucuronic Acid, Mg.
E. L.	9	M	700	51	150
R. R.	8	M	640	51	213
P. J.	7	M	1,110	65	361
J. W.	13	M	1,060	55	479
W. W.	6	M	640	65	207
B. M.	9	F	550	100	240
R. L.	9	F	310	92	159
D. S.	5	F	690	30	285
G. C.	13	F	1,060	31	209
M. D.	6	F	800	51	242
K. L.	6	F	260	67	166
L. G.	11	F	510	47	164
C. W.	11	F	890	81	321
M. D.	11	F	580	60	211
C. L.	5	F	690	66	223
R. S.	10	M	566	39	216
W. Z.	10	M	540	44	250
T. S.	8	M	670	25	190
M. S.	8	M	310	55	113
P. C.	13	M	930	24	261
G. W.	8	M	570	22	138
C. S.	7	M	655	60	170
D. S.	5	M	330	42	156
K. D.	6	M	170	70	99
Average	8.4	..	...	54	231

Patients: The patients used in this study had all been thoroughly studied and their conditions diagnosed as rheumatic fever by members of the staff of La Rabida Jackson Park Sanatorium, Chicago, for children with rheumatic fever. The normal children and the patients with nonrheumatic disease resided chiefly in a home for orphans.

Diet: The diet was institutional in character and was adequate according to all known standards. Since the menus were institutionalized, it was assumed that for this study placement of the children on a constant diet was unnecessary.

3. Dische, Z.: A New Specific Color Reaction of Hexuronic Acid, J. Biol. Chem. **167**:189, 1947.

The questions of the acceptance of foods and drugs and the collection of the morning or twenty-four hour specimens of urine did not constitute a problem because of the excellent cooperation of the children.

Results.—Urinary Output (Twenty-Four Hour) of Glucuronic Acid in Normal Children: The urine of 24 normal children (14 boys and 10 girls), ranging in age from 5 to 13 years (average, 8.4 years), was collected for twenty-four hours. The morning sample of "fasting" urine was kept separate from the other collections.

The results are shown in table 1 and reveal that the average twenty-four hour output was 231 mg., the range being from 99 to 361 mg., with

TABLE 2.—*Data Obtained on Forty-Seven Children with Rheumatic Fever and Various Complications*

No. of Patients	Diagnosis	Range of Glucuronic Acid, Mg.	Average Output, Mg./24 Hr.*
5	Severe rheumatic fever and rheumatic heart disease	286 to 625	481
4	Moderately severe rheumatic fever and rheumatic heart disease	205 to 312	267
3	Potential or mild rheumatic fever and rheumatic heart disease	258 to 281	269
6	Moderately severe rheumatic fever	152 to 480	287
5	Mild rheumatic fever	126 to 513	241
4	Inactive or potential rheumatic fever	110 to 490	260
4	Moderately severe to mild rheumatic heart disease	131 to 392	278
3	Chorea	190 to 470	315
3	Chronic sinusitis; chronic pharyngitis; tonsillitis	253 to 448	344
11	Acetylsalicylic acid, 2.66 Gm. daily administered for rheumatic fever or rheumatic fever and rheumatic heart disease	562 to 1,900	1,070

* The average output of glucuronic acid of 18 children with the "active" disease was 321 mg.; of 16 with the "inactive" form, 267 mg.; of 3 nonrheumatic children, 237 mg., and of 11 receiving acetylsalicylic acid, 1,070 mg.

one "spurious" value of 479 mg. The overnight "fasting" urine specimen yielded an average concentration of 54 mg. per hundred cubic centimeters, the range being from 22 to 102 mg.

Urinary Output (Twenty-Four Hour) of Glucuronic Acid by Children with Rheumatic Fever: The concentration of glucuronic acid in the overnight "fasting" specimen was determined for 50 children with rheumatic fever and its complications in various degrees of activity. This was done for exploratory reasons. The results, which need not be cited, were within the normal range as shown in table 1, except for those children who were receiving acetylsalicylic acid.

The urine was collected for a period of twenty-four hours from 47 children with rheumatic fever with various complications and degrees of activity, and from 3 children with tonsillitis, sinusitis and pharyngitis, 22 being boys and 28 girls. The children ranged in age from 5 to 13 years and all received the same nutritious institutional diet.

The results are shown in table 2. The average output of the 16 children with the "inactive" disease was 267 mg., which is not significantly different statistically from the 231 mg. observed for the normal children. The output was elevated in 18 children with the "active" disease, the average being 321 mg.; however, the output was also increased in 1 child with tonsillitis, 1 with sinusitis and 1 with pharyngitis. The only definitely significant observation was the pronounced increase in the output of glucuronic acid in patients receiving acetylsalicylic acid.

A study of the urinary output of glucuronic acid of both the normal and the rheumatic children showed that it was not related to sex and age in the age range studied.

Comment.—The preceding results revealed that the output of glucuronic acid in the urine was not specifically increased in children with rheumatic fever, and if increased it was not strikingly so. However, the urinary excretion of glucuronic acid was decidedly elevated after administration of salicylic acid. These observations confirmed those in reports in the literature [4] and stimulated us to study the effect of the administration of sodium bicarbonate on the blood level of salicylates and the output of salicylic acid and glucuronic acid in urine. It was thought that since sodium bicarbonate brings about excretion of salicylic acid in the urine it might have an interesting effect on the excretion of glucuronic acid.

EFFECT OF ADMINISTRATION OF SODIUM BICARBONATE WITH ACETYLSALICYLIC ACID ON THE PLASMA LEVEL OF SALICYLATES AND THE OUTPUT OF SALICYLIC AND GLUCURONIC ACID IN THE URINE

Experimental Methods.—Subjects: Group A: For this work 15 patients, 8 boys and 7 girls, ages ranging from 6 to 14 years, who had had rheumatic fever but who at the time of study manifested no evidence of rheumatic activity, were selected to receive acetylsalicylic acid only.

Group B: A similar group of 14 additional patients was selected to receive acetylsalicylic acid with sodium bicarbonate.

All the patients received the same diet. The twenty-four hour urinary output was collected for three or four days prior to, during and after the period of administration, and all tests were performed during these precontrol and postcontrol

4. Salt, H. B.: Application to Urine of Tollen's Naphthoresorcinol Test for Conjugated Glycuronides, Biochem. J. **29**:2705, 1935. Quick, A. J.: Conjugation of Salicylic Acid with Glycine and Its Action on Uric Acid Excretion, J. Biol. Chem. **101**:475, 1933.

periods. The patients had previously been studied extensively by the usual clinical methods of examination.

Tests Performed: Blood salicylates were determined by the method of Brodie and his associates [5] using plasma and by Peter's [6] method using serum. The average salicylate level was only 2 to 3 mg. per hundred cubic centimeters higher when the plasma method was used; our figures represent values obtained for blood serum. The carbon dioxide-combining power was determined by Van Slyke's [7] manometer method, the prothrombin time by Quick's [8] method, p_H of the blood by the Beckman p_H meter, values for urinary salicylates by Peter's [6] method and glucuronic acid content of the urine by Dische's [3] method.

Plan of Drug Administration: Acetylsalicylic acid alone was given to the patients in group A, and acetylsalicylic acid plus sodium bicarbonate in a ratio of 1 to 2 was given to the patients in group B.

Both groups received the salicylic acid according to the following program: After three or four days of control, the patient received 1.2 Gm. per day (0.3 Gm. every six hours) for four days, 2.4 Gm. per day (0.6 Gm. every six hours) for the second four days, then 3.6 Gm. per day (0.6 Gm. every four hours) for the third four days and, finally, 4.8 Gm. per day (0.6 Gm. every three hours) for four days. However, if significant symptoms of salicylism occurred, or when the blood salicylate level rose above 25 to 30 mg. per hundred cubic centimeters, use of the drug was discontinued. The blood determinations were made at the end of each fourth day of study; the other determinations were made daily.

Results.—Salicylism: Eight of the 15 patients in group A, not receiving sodium bicarbonate, showed some symptoms of salicylism. In 6 the symptoms were quite definite (table 3) and occurred when the plasma level of salicylate was 20 mg. per hundred cubic centimeters or above.

Only 3 of the 14 patients in group B, receiving sodium bicarbonate, showed symptoms of salicylism, and these were mild.

Blood Plasma Salicylate Concentration: It should be noted by inspection of the data in tables 3 and 4 that the plasma salicylates rose at a somewhat different rate in different patients receiving the same dose and that the administration of sodium bicarbonate resulted in a definite decrease in the plasma level of salicylates.

Carbon Dioxide–Combining Power of Blood Plasma: The average p_H of the plasma of the subjects receiving acetylsalicylic acid alone was 7.41, and of those receiving sodium bicarbonate in addition it was 7.46.

5. Brodie, B. B.; Udenfriend, S., and Coburn, A. F.: Determination of Salicylic Acid in Plasma, J. Pharmacol. & Exper. Therap. **80**:114, 1943.

6. Peter, J. T.: Easy and Accurate Method of Determination of Serum and Urine Salicylate Levels During Treatment with Salicyl Drugs, Acta med. Scandinav. **129**:299, 1947.

7. Van Slyke, cited by Hawk, P. B.; Oser, B. L., and Summerson, W. H.: Practical Physiological Chemistry, ed. 12, Philadelphia, The Blakiston Company, 1947, p. 625.

8. Quick, A. J.: Determination of Prothrombin Time, Am. J. Physiol. **140**: 212, 1943.

TABLE 3 (Group A).—*Relation of Plasma and Urinary Salicylate and Urinary Glucuronide on the Administration of Acetylsalicylic Acid Alone**

Name	Age, Years	Body Weight, Kg.	Blood Salicylate Concentration, Mg./100 Cc. Days 1 to 4	5 to 8	9 to 12	13 to 16	Total ASA Intake, Gm.	Urinary Output of Salicylates, Gm. Days 1 to 4	5 to 8	9 to 12	13 to 16	Total Urine Salicylate Output, Gm.	Glucuronide, Gm. Days 1 to 4	5 to 8	9 to 12	13 to 16	Total Glucuronic Acid in Urine, Gm.
F. F.†	13	45.7	0.5	5.0	16.0	35.5	44.4	3.14	5.09	6.50	10.0	24.8	2.77	4.12	5.89	9.82	22.6
C. R.†	9	27.4	1.0	9.0	25.0	39.2	35.4	2.09	3.29	4.40	2.98	12.8	1.98	3.37	5.88	3.78	15.2
L. G.	9	30.0	0	9.5	10.0	21.5	36.0	2.27	6.33	6.13	3.40	18.0	1.48	3.22	3.93	2.47	11.1
Average	..	....	0.5	7.8	17.7	35.7	38.6	2.50	4.87	5.77	....	18.5	2.08	3.57	5.23	5.35	16.3
C. W.†	12	32.4	0.5	22.0	30.0	....	28.2	2.50	3.78	6.30	....	12.4	2.00	4.32	8.16	....	15.4
C. M.	14	41.3	2.0	15.5	38.0	....	27.6	2.80	4.55	8.17	....	15.5	2.40	4.02	7.29	....	13.7
D. M.	10	34.6	0.5	15.4	33.0	....	26.4	3.11	5.46	6.16	....	14.7	2.41	3.15	5.36	....	10.9
E. H.	9	28.4	1.5	13.5	42.0	....	26.4	3.10	5.21	7.35	....	13.6	2.54	3.84	5.93	....	9.2
R. K.†	8	24.8	2.5	20.4	54.0	....	26.4	3.13	6.23	8.01	....	17.3	1.83	3.54	5.67	....	11.0
J. H.†	12	36.2	0	11.5	29.2	....	25.8	3.12	5.21	7.35	....	15.7	2.54	3.84	5.93	....	12.3
F. L.	13	54.0	0	8.0	25.5	....	30.0	4.73	6.24	7.59	....	18.5	2.23	4.04	6.83	....	13.1
G. P.†	9	31.4	0	16.2	38.5	....	27.0	4.06	5.44	6.72	....	16.2	2.26	3.26	5.84	....	11.3
Average	..	....	0.9	15.3	37.4	....	27.2	3.82	5.36	7.20	....	15.5	2.40	3.75	6.37	....	12.1
C. N.	12	50.5	3.5	37.0	....	....	20.4	2.84	7.10	....	....	10.0	2.81	7.16	....	....	11.0
E. A.	6	21.5	7.0	34.0	....	....	14.4	2.10	4.42	....	....	6.5	1.40	2.80	....	....	4.2
J. W.	8	27.8	2.5	26.0	....	....	14.4	2.62	5.49	....	....	8.0	1.69	3.50	....	....	5.2
H. C.	7	29.2	5.0	27.5	....	....	14.4	2.60	5.33	....	....	7.9	2.68	5.07	....	....	7.8
Average	..	....	4.5	31.1	....	....	15.9	2.80	5.56	....	....	8.2	2.39	4.65	....	....	7.1
Average of all	..	....	1.8	18.0	....	....	....	2.80	5.30	....	....	....	2.30	4.00	....	....	....

* Dosage of acetylsalicylic acid (ASA) was as follows: 1 to 4 days, 0.3 Gm. four times daily every six hours; 5 to 8 days, 0.6 Gm., four times daily every six hours; 9 to 12 days, 0.6 Gm., six times daily every four hours; 13 to 16 days, 0.6 Gm., eight times daily every three hours.

† Salicylism developed in these patients. F. F. had tinnitus on the fifteenth day after 39.0 Gm. of ASA. C. R. had slight hyperpnea on thirteenth day after 35.4 Gm. of ASA; respirations increased from 18 to 28 per minute. C. W. vomited on thirteenth day after 28.2 Gm. of ASA and had tinnitus on twelfth day. R. K. vomited with slight elevation in temperature on thirteenth day after 26.4 Gm. of ASA. J. H. had tinnitus on eleventh day after 19.2 Gm. of ASA. G. P. vomited on eleventh day after 19.2 Gm. of ASA.

TABLE 4 (Group B).—*Relation of Plasma and Urinary Salicylate and Urinary Glucuronide on the Administration of Acetylsalicylic Acid with Sodium Bicarbonate (1:2)* *

Name	Age, Years	Body Weight, Kg.	Blood Salicylate Concentration, Mg./100 Cc. Days 1 to 4	5 to 8	9 to 12	13 to 16	Total ASA Intake, Gm.	Urinary Output of Salicylates, Gm. Days 1 to 4	5 to 8	9 to 12	13 to 16	Total Urine Salicylate Output, Gm.	Glucuronide, Gm. Days 1 to 4	5 to 8	9 to 12	13 to 16	Total Glucuronic Acid in Urine, Gm.
L. G.	9	31.1	0	10.2	20.5	27.0	41.6	4.1	6.2	9.1	18.0	37.6	2.4	2.8	3.2	5.2	13.6
J. B.†	11	52.5	0	6.0	17.5	24.0	40.2	3.6	6.4	8.2	13.1	31.5	2.2	2.4	2.6	4.5	13.7
L. A.	13	50.7	1.0	10.2	18.5	27.5	45.0	2.4	6.5	5.1	14.2	32.2	2.3	2.4	2.8	5.6	15.1
E. J.	12	48.0	0	5.0	18.0	29.0	48.0	2.9	6.7	9.8	13.0	35.4	2.1	2.0	2.7	5.9	12.8
J. G.†	6	18.8	2.5	11.0	19.0	24.5	45.0	4.0	6.8	10.7	15.7	37.2	1.3	1.7	2.0	2.5	7.7
M. G.	7	36.6	0	7.5	20.0	22.5	45.0	3.9	7.6	10.6	18.3	40.6	2.0	2.9	3.1	4.7	12.9
R. C.	11	45.0	0	5.5	16.0	22.0	45.0	3.8	6.3	11.8	15.5	37.4	1.6	2.1	2.6	3.4	9.7
First 7 (Average)	..	....	0.6	7.9	18.5	25.2	45.5	3.8	6.6	9.3	15.7	36.0	2.0	2.7	3.1	1.4	12.3
R. K.	8	26.4	1.0	10.0	21.0	....	27.6	4.4	6.9	10.2	....	21.6	2.2	2.6	3.2	...	8.0
H. C.	7	20.8	3.0	14.0	23.0	....	27.6	3.2	5.6	9.3	....	18.1	1.8	2.0	4.2	...	9.0
S. F.	7	22.5	3.0	20.5	29.5	....	27.6	3.4	6.2	11.2	....	20.7	1.8	2.5	3.7	...	8.3
M. K.	9	24.8	6.0	12.4	25.0	....	22.4	4.0	6.6	12.9	....	23.5	2.1	2.1	3.7	...	7.9
C. G.	9	32.8	10.0	15.5	28.5	....	28.8	2.3	6.2	9.1	....	18.6	2.4	2.2	4.2	...	9.8
G. W.	5	19.4	3.0	13.0	24.0	....	27.0	3.7	6.1	9.2	....	19.0	1.3	2.0	2.5	...	5.8
B. G.†	6	28.0	0	6.0	15.5	....	27.6	2.8	6.7	9.7	....	19.2	1.9	2.7	3.4	...	8.0
Last 7 (Average)	..	....	3.7	13.0	25.2	....	28.3	3.5	6.3	10.2	....	20.1	1.9	2.6	3.5	...	8.01
Average for all	..	....	2.2	10.5	21.8	....	36.9	3.7	6.5	9.5	....	28.0	1.96	2.7	2.35	...	10.2

* Dosage of acetylsalicylic acid (ASA) was the same as given in table 3, except that one part ASA was given with two parts sodium bicarbonate.

† Salicylism developed in these patients. J. B. had tinnitus on fourteenth day after 34.3 Gm. of ASA plus sodium bicarbonate. J. G. had epistaxis on twelfth day after 28.2 Gm. of ASA plus sodium bicarbonate. B. G. had nausea on fourteenth day after 34.2 Gm. of ASA plus sodium bicarbonate.

In the patients in group A, a high correlation (0.9) was found between the carbon dioxide-combining power of the plasma and the plasma salicylate level (figure). The patient with hyperpnea had a carbon dioxide-combining power of only 37 volumes per cent and a plasma p_H of 7.5 due to the blowing off of carbon dioxide.

Prothrombin Time: A prolongation of the prothrombin time was not seen in any of our patients, though such is reported to occur.[9]

Urine Determinations: The p_H of the urine remained acid consistently. The amount of urine increased slightly the first three or four days and then decreased, probably because of perspiration.

Most patients had cleared their body of salicylate within two days and all within four days after cessation of administration. When sodium

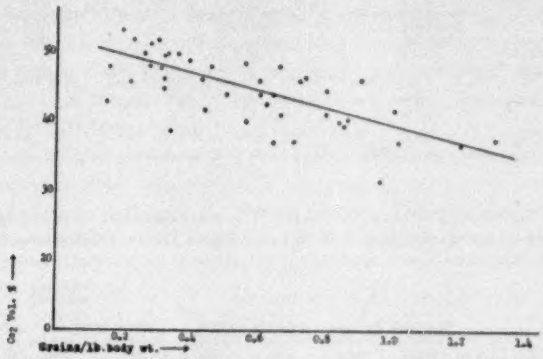

Chart showing correlation between amount of acetylsalicylic acid given daily (in grains per pound of body weight) and the carbon dioxide-combining power (in volumes per cent).

bicarbonate was given with the acetylsalicylic acid, the salicylate was cleared from the body within two days in all patients.

9. Owen, G. C., and Bradford, H. A.: Prothrombinopenic Effect of Massive Salicylate Therapy in Acute Rheumatic Fever, Ann. Int. Med. **25**:97, 1946. Fashena, G. J., and Walker, J. N.: Salicylate Intoxication: Studies on the Effect of Sodium Salicylate on Prothrombin Time and Alkali Reserve, Am. J. Dis. Child. **68**:369 (Dec.) 1944. Clausen, F. W., and Jager, B. V.: Relation of the Plasma Salicylate Level to the Degree of Hypothrombinemia, J. Lab. & Clin. Med. **31**: 428, 1946. Govan, C. D.: Effect of Salicylate Administration on the Prothrombin Time, J. Pediat. **29**:629, 1946. Butt, H. R.; Leake, W. H.; Solley, R. F.; Griffith, C. G.; Huntington, R. W., and Montgomery, H.: Studies in Rheumatic Fever: Physiologic Effect of Sodium Salicylate on the Human Being, with Particular Reference to Prothrombin Level of the Blood and the Effect on Hepatic Parenchyma, J. A. M. A. **128**:1195 (Aug. 25) 1945. Manchester, R. C.: Rheumatic Fever in Naval Enlisted Personnel: The Physiologic and Toxic Effect of Intensive Salicylate Therapy in Acute Cases, ibid. **131**:209 (May 18) 1946.

Urinary Excretion of Salicylate and Glucuronic Acid: The results on the excretion of salicylate and glucuronic acid with and without the administration of sodium bicarbonate with the acetylsalicylic acid are shown in tables 5 and 6.

When acetylsalicylic acid alone was taken, the average excretion of salicylic acid in 8 patients was 56 per cent (range, 36 to 66 per cent). When essentially the same amount of acetylsalicylic acid was taken with two parts of sodium bicarbonate by 7 patients, the average excretion of salicylic acid was 70 per cent (range, 65 to 82 per cent).

TABLE 5.—*Summary of Comparable Results from Tables 3 and 4*

	Total Salicylic Acid, Gm.	Blood Salicylate Concentration, Mg./100 Cc. Days			Urine Output of Salicylic Acid, Gm. Days			Total Output	Urine Output of Glucuronic Acid, Gm. Days			Total Output	Per Cent of Salicylate Excreted in Urine
		1 to 4	5 to 8	9 to 12	1 to 4	5 to 8	9 to 12		1 to 4	5 to 8	9 to 12		
Acetylsalicylic acid.....	27.2	0.9	15.3	37.4	3.8	5.3	7.2	15.5	2.4	3.7	6.4	12.1	56
Acetylsalicylic acid + sodium bicarbonate.....	28.2	3.7	13.0	25.2	3.5	6.3	10.2	20.1	1.9	2.6	3.5	8.0	71

TABLE 6.—*Urinary Excretion of Salicylic Acid and Glucuronic Acid on Administration of Acetylsalicylic Acid With and Without Sodium Bicarbonate (1:2)*

	Total Salicylate Intake, Gm.	Total Salicylate Output, Gm.	Total Glucuronide Output, Gm.	Salicylic Glucuronide, Gm.	Free Salicylate, Gm.	Salicylate Excreted as Glucuronide, Gm.	Per Cent Free Salicylate
Acetylsalicylic acid...	27.2	15.5	8.6*	14.66	9.44	6.06	55.4
Acetylsalicylic acid + sodium bicarbonate	28.2	20.1	4.5*	7.70	16.90	3.20	84.0

* Corrected for a control output of glucuronic acid before salicylic acid therapy in this group of patients which amounted to 0.39 mg. per day, or 2.50 Gm. for twelve days.

Reference to the data in table 6 will show that the sodium bicarbonte increased the excretion of free salicylate in the urine and decreased the excretion of glucuronic acid. In other words, the sodium bicarbonate, while increasing the excretion of salicylic acid, decreased decidedly the amount of salicylic acid excreted as the glucuronide.

COMPARISON OF THE EXCRETION OF GLUCURONIC ACID ON ADMINISTRATION OF ACETYLSALICYLIC ACID TO PATIENTS DURING AN EXACERBATION AND A REMISSION OF RHEUMATIC FEVER

Four patients, 7 to 11 years of age, with an acute exacerbation of rheumatic fever were given 17.1 Gm. of acetylsalicylic acid for ten days. An average of 40 per cent, or 6.84 Gm., of salicylic acid was excreted in

the urine. The average total amount of glucuronic acid excreted was 6.9 Gm., or 40.0 per cent of the amount of salicylic acid given. Four patients, 6 to 12 years of age, in a remission were given 20.8 Gm. of acetylsalicylic acid for fourteen days, and they excreted an average of 50 per cent of the salicylate in the urine. At the same time they excreted an average of 8.7 Gm. of glucuronic acid, or 42 per cent of the amount of salicylic acid given. Thus, the ability to form salicylic glucuronide was similar in both groups of patients.

RELATION BETWEEN THE EXCRETION OF GLUCURONIC ACID AND ERYTHROCYTE SEDIMENTATION RATE

The data on urinary excretion of glucuronic acid were studied to ascertain whether they might be correlated with the erythrocyte sedimentation rate. Like the data in table 2, the results of the correlation showed that the excretion of glucuronic acid was higher by those patients with a high average sedimentation rate and the active manifestations of the disease. However, the correlation was not definite enough to be of significant prognostic value.

Effect of Administration of Ascorbic Acid (Vitamin C) on the Output of Glucuronic Acid.—Ascorbic acid was administered to 4 patients with active symptoms and signs of rheumatic fever. The dose was gradually increased from 300 to 600 mg. per day over a period of three days, the experiment lasting a total of six days.

The results showed that administration of ascorbic acid had no influence on the urinary excretion of glucuronic acid.

COMMENT

This investigation was undertaken with the hope that some alteration in glucuronic acid metabolism might be observed in patients with rheumatic fever which would specifically assist in the differential diagnosis of rheumatic fever. This hope was not realized.

Though the urinary excretion of glucuronic acid was increased on the average in patients with rheumatic fever having acute manifestations of the disease, the increase was not specific, because patients with tonsillitis, sinusitis and pharyngitis also showed a definite rise. Furthermore, though the average urinary excretion of glucuronic acid by the child with inactive rheumatic fever was somewhat greater than that of the normal child without a history of rheumatic fever, the difference was not statistically significant. However, if a large number of patients was studied, the difference might become statistically significant. Nevertheless, if this was true, such a fact would be of no value in differential diagnosis.

When we studied the excretion of glucuronic acid on the administration of acetylsalicylic acid with and without sodium bicarbonate, we found no new knowledge which might assist in the differential diagnosis. Our results on the plasma level of salicylic acid and on the excretion of salicylic acid with and without the concomitant administration of sodium bicarbonate confirmed results reported in the literature.[10] In addition, our results showed that when the sodium bicarbonate decreases the plasma level of salicylic acid and increases the urinary excretion of salicylic acid it increases the urinary excretion of unconjugated salicylic acid, of salicylic acid or of salicylic glucuronide. It appears, therefore, that administration of sodium bicarbonate (*a*) directly decreases the conjugation of salicylic acid with glucuronic acid in the liver, or (*b*) facilitates the excretion of salicylic acid by the kidney and at a lower plasma level of salicylic acid less salicylic glucuronide is formed, or (*c*) both. If the first was true, then more unconjugated salicylic acid would enter the systemic circulation and be eliminated in the urine, causing a decreased plasma level; this interpretation requires the assumption that the kidney does not excrete salicylic glucuronide as readily as unconjugated salicylic acid in the form of the free acid or mineral salt.

In either case the administration of sodium bicarbonate with acetylsalicylic acid decreases the demand for glucuronic acid synthesis. Speculation regarding the therapeutic implications of these observations and their relation to the mechanism of the action of salicylates in rheumatic fever is not warranted in the absence of data on the relative rate of renal clearance and therapeutic effectiveness of intravenously administered salicylic acid and salicylic glucuronide.

SUMMARY

1. The metabolism of glucuronic acid with and without the administration of acetylsalicylic acid, with or without sodium bicarbonate, is not specifically altered in patients with rheumatic fever to the extent that such alteration might be used for differential diagnosis.

2. The average twenty-four hour urinary excretion of glucuronic acid in 24 children (5 to 13 years of age) without a history of rheu-

10. Smull, K.; Wégria, R., and Leland, J.: Effect of Sodium Bicarbonate on Serum Salicylate Level During Salicylate Therapy of Patients with Acute Rheumatic Fever, J. A. M. A. **125**:1173 (Aug. 26) 1944. Coombs, F. S.: Toxicity of Salicylates, News Letter, Army Air Forces Rheumatic Fever Control Program, **2**:11, 1945. Keith, J. D., and Ross, A.: Observations on Salicylate Therapy in Rheumatic Fever, Canad. M. A. J. **52**:554, 1945. Smith, P. K.; Gleason, H. L.; Stoll, C. B., and Orgorzalek, S.: Studies on the Pharmacology of Salicylates, J. Pharmacol. **87**:237, 1946; abstracted, Federation Am. Soc. Exper. Biol. **5**:203, 1946. Morris, N., and Graham, S.: The Value of Alkali in Salicylate Therapy, Arch. Dis. Childhood **6**:273, 1931.

matic fever was 231 mg., the range being 99 to 361 mg. The average twenty-four hour urinary output of 16 children with inactive rheumatic fever (5 to 13 years of age) was 267 mg.; this is not significantly greater than that observed for normal children. The average twenty-four hour output of 11 children with active rheumatic fever (5 to 13 years of age) was 321 mg.; this is a definite though not a specific increase, since a similar increase was seen in children with tonsillitis, sinusitis and pharyngitis.

3. The administration of acetylsalicylic acid without sodium bicarbonate definitely increases the twenty-four hour urinary excretion of glucuronic acid.

4. The administration of two parts of sodium bicarbonate with one part of acetylsalicylic acid to children with inactive and with active rheumatic fever causes in both types of patient a similar decrease in the plasma level of salicylic acid, a similar increase in the total urinary excretion of salicylic acid and a similar decrease in the excretion of glucuronic acid. Sodium bicarbonate, when augmenting the total urinary excretion of salicylic acid, decreased the amount excreted as the glucuronide.

5. Administration of ascorbic acid had no significant effect on excretion of glucuronic acid in the urine of patients with rheumatic fever.

6. No difference in the ability of children with active and with inactive rheumatic fever (without obvious hepatic damage) to synthesize and excrete glucuronic acid in response to administration of acetylsalicylic acid was observed.

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PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA IN INFANCY

Review of Treatment and Report on an Infant Treated with Methacholine (Mecholyl®) Chloride

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AND

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IN 1941, Hubbard[1] called attention to the fact that in infancy paroxysmal tachycardia is a somewhat different and distinctive clinical entity. Limiting himself to cases in which there were graphic demonstration of the tachycardia and no other accompanying illness, he gathered 19 cases from the literature, all of children under the age of 1 year, and presented 9 cases of his own. The heart rates varied from 220 to 305; all beats were supraventricular in origin, and in no case was there clear proof of auricular flutter.

The picture in infants is much more serious than that in adults. If the tachycardia continues, congestive failure develops, and it is usually the symptoms of failure, although they are not always recognized as such, that draw the attention of the parent or physician to the fact that the baby is ill.

In the typical case one finds vomiting suggestive of pyloric stenosis. The baby becomes limp and gray, obviously prostrated. The heart rate is rapid and difficult to determine. The heart enlarges rapidly and becomes greatly dilated and, if this dilatation persists, congestive failure develops. There are severe dyspnea, enlargement of the liver and spleen, abdominal distention and, possibly, elevation in the temperature to 102 F. and leukocytosis. The roentgenogram of the chest shows cardiac enlargement and pulmonary congestion. The attack may stop spontaneously or go on to death if proper treatment is not given. When the tachycardia stops, all symptoms promptly subside.

Hubbard[1] considered administration of digitalis the treatment of choice, with pressure on the carotid sinuses and eyeballs or induction of vomiting rarely effective in children. Use of methacholine (mecholyl®) was to be considered only when treatment with digitalis

1. Hubbard, J. P.: Paroxysmal Tachycardia and Its Treatment in Young Infants, Am. J. Dis. Child. **61**:687 (April) 1941.

failed. Goodman and Gilman,[2] on the other hand, stated that methacholine therapy and pressure on the carotid sinus are to be tried first. If these fail, quinidine may be employed before digitalis is used. They, however, as most discussants on paroxysmal tachycardia, were considering the disease in general and were not especially concerned with infants. This applies to Barker, Wilson, Johnson and Wishart,[3] who were of the opinion that the giving of digitalis in large amounts often restores normal rhythm. Administration of quinidine and quinine is somewhat less effective but may give good results even though digitalis treatment failed; use of methacholine and acetylcholine was ineffectual. Their discussion involved 35 patients, only 2 of whom were under 10 years of age, and no infants. They expressed the view that most of the features of auricular paroxysmal tachycardia can be accounted for by circus rhythm involving either the sinoauricular node or the auriculoventricular node. This view they have advanced on several occasions.[4]

Various other drugs have been used which may or may not apply to infants. Zindahl[5] and Boyd and Scherf[6] advocated use of magnesium sulfate intravenously in a 20 to 25 per cent solution in treatment of paroxysmal tachycardia. Phenylephrine (neo-synephrine®) hydrochloride was used by Youmans, Goodman and Gould,[7] who considered that a moderate, sudden, brief rise in blood pressure produced by intravenous injection of this vasoconstrictor drug might reflexly stop a paroxysmal or nodal tachycardia. It gave good results in 4 patients. Lanatoside C, a glycoside obtained from digitalis, was used successfully by Limper[8] three times in an infant in whom there had been no response to treatment with digitalis or quinidine.

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2. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics: A Textbook of Pharmacology, Toxicology and Therapeutics for Physicians and Medical Students, New York, The Macmillan Company, 1941, p. 533.

3. Barker, P. S.; Wilson, E. N.; Johnson, F. D., and Wishart, S. W.: Auricular Paroxysmal Tachycardia with Auriculoventricular Block, Am. Heart J. **25**:765 (June) 1943.

4. Barker, P. S.; Wilson, F. N., and Johnson, F. D.: The Mechanism of Auricular Paroxysmal Tachycardia, Am. Heart J. **26**:435 (Oct.) 1943. Barker, P. S.; Johnson, F. D., and Wilson, F. N.: Auricular Paroxysmal Tachycardia with Alteration of Cycle Length, ibid. **25**:799 (June) 1943.

5. Zindahl, W. T.: Magnesium Sulfate in Paroxysmal Tachycardia, Ann. Int. Med. **25**:531 (Sept.) 1946.

6. Boyd, L. J., and Scherf, D.: Magnesium Sulfate in Paroxysmal Tachycardia, Am. J. M. Sc. **206**:43 (July) 1943.

7. Youmans, W. B.; Goodman, M. J., and Gould, J.: Treatment of Paroxysmal Auricular or Nodal Tachycardia with the Vasopressor Drug Neosynephrine, Proc. Soc. Exper. Biol. & Med. **64**:380 (March) 1947.

8. Limper, M. A.: Recurrent Paroxysmal Tachycardia in a Young Infant, Am. J. Dis. Child. **77**:753 (June) 1949.

Hobbs [9] reported on an infant with the first attack of paroxysmal tachycardia at the age of 2 months, who had six more attacks at intervals of three to forty-seven days which responded to digifolin® given subcutaneously, one to four doses being required each time.

Scott and Limper [10] reported on an infant who responded to digifolin® and on another infant who responded to quinine administered intravenously in the first few attacks. However, in the last attack, with a larger dosage, this infant had laryngeal spasm and died. Others [11] have reported cases of infants who died before therapy could be instituted. One had a ventricular rate of 365 per minute.

Having an effect similar to that of methacholine (acetyl-beta-methylcholine) in the treatment of paroxysmal tachycardia is acetylcholine. Philipsborn and Gibson [12] reported on 2 infants treated successfully with acetylcholine bromide given intravenously, although 1 infant died from presumably unrelated extensive cerebral hemorrhage. On experimental animals they observed that the drug caused partial or complete heart block and ventricular standstill of varying duration. In addition, the drug caused slight depression of the sinoauricular node and more pronounced depression of the auricular musculature, the auriculoventricular node and the bundle of His. These actions, along with a vagal braking action, are favorable for abolishing paroxysmal supraventricular tachycardia. The authors recommended this treatment as an alternate method, should digitalis fail in a reasonable period of time or for desperately ill patients requiring immediate relief. Abbott [13] mentioned 5 cases in which 0.1 Gm. of acetylcholine given intravenously stopped paroxysmal tachycardia. He was of the opinion that there were few, if any, of the terrific side effects seen with methacholine. Subcutaneous administration of acetylcholine is useless.[14]

Methacholine has been used infrequently in the treatment of paroxysmal supraventricular tachycardia in children. Starr was able to abolish the tachycardia in 80 per cent of the attacks treated, as he

9. Hobbs, L. F.: Paroxysmal Tachycardia in Infancy, Am. Heart J. **21**:804 (June) 1941.

10. Scott, E. P., and Limper, M. A.: Paroxysmal Tachycardia: Report of Two Cases in Infants, J. Pediat. **29**:96 (Jan.) 1946.

11. Edeiken, J.: Extreme Tachycardia, Am. J. M. Sc. **203**:52 (Jan.) 1943. Silverman, J. J., and Race, O. M.: Paroxysmal Tachycardia with a Ventricular Rate of 365 per Minute, Am. Heart J. **37**:1139 (Jan.) 1949.

12. Philipsborn, H. F., Jr., and Gibson, S.: Paroxysmal Tachycardia in Infants, Pediatrics **1**:205 (Feb.) 1948.

13. Abbott, K. H.: Acetylcholine in Paroxysmal Tachycardia, Correspondence, J. A. M. A. **113**:1243 (Sept. 23) 1939.

14. Starr, I.: Acetylcholine in Paroxysmal Tachycardia, Correspondence, J. A. M. A. **113**:527 (Aug. 5) 1939.

reported in 1933 [15] and 1936.[16] All his patients were adults. He treated seventy-five attacks in 37 patients. In 58 per cent the action of the drug was successful alone. Twenty per cent required, in addition, pressure on the carotid sinus and 22 per cent of the attacks required second larger doses of the drug. Wright [17] reported on a 6 year old girl who had had eight previous attacks of paroxysmal tachycardia, beginning at the age of 9 months, which had subsided spontaneously after lasting two days to two weeks. She then had another attack which responded in four minutes to 5 mg. of methacholine given subcutaneously. She later had seventeen more attacks, two subsiding spontaneously and the others responding to 10 to 100 mg. of methacholine. The 100 mg. dose was accidental but had no bad effect. Five to 40 mg. was the usual dose. He expressed his view that treatment with quinine, digitalis and quinidine has not generally met with success.

We should like to present a case of paroxysmal supraventricular tachycardia in infancy which we believe to be the first reported in which methacholine was used successfully to abolish the tachycardia in infancy.

REPORT OF A CASE

This infant was born on Jan. 25, 1949. She was the product of a nine month gestation and a three hour labor. There were no apparent abnormalities. The weight at birth was 6 pounds 3¼ ounces (2,814 Gm.). The mother and baby went home when the baby was 5 days old. She was receiving a routine evaporated milk formula. At the age of 12 days there was a sudden onset of vomiting which continued with every feeding, and the baby was admitted to the hospital two days later. At this time there was a questionable mass in the right upper quadrant and some peristaltic waves were seen. Blood and urine examinations gave essentially normal results. Roentgenologic study showed a large gas bubble and considerable fluid in a distended stomach, with practically no gas seen elsewhere in the abdomen. There was some increased density, which was either pneumonitis or atelectasis, in the upper and lower portions of the right lung. The heart was not remarkable. At age of 16 days a pylorotomy was performed, at which time a well developed tumor, 2.5 by 1 cm., was observed. Postoperative convalescence was uneventful.

Examination on a routine office visit at the age of 2 months showed the infant to be doing well; she weighed 8 pounds 9 ounces (3,884 Gm.). A mixture of atropine sulfate and phenobarbital was prescribed for a mild colic.

At the age of 10 weeks the infant started taking only one-half her usual amount of formula. This persisted with no irritability or fussing for two days, when the baby was seen and hospitalized. Physical examination showed a well developed and well nourished baby, slightly pale and breathing rapidly, but not cyanotic.

15. Starr, I., Jr.: Acetyl-β-Methylcholin: Its Action on Paroxysmal Tachycardia and Peripheral Vascular Disease, with Discussion of Its Action in Other Conditions, Am. J. M. Sc. **186**:330 (Sept.) 1933.

16. Starr, I., Jr.: Acetyl-β-Methylcholin: Further Studies of Its Action in Paroxysmal Tachycardia and in Certain Other Disturbances of Cardiac Rhythm, Am. J. M. Sc. **191**:210 (Feb.) 1936.

17. Wright, F. H.: Paroxysmal Nodal Tachycardia Treated with Mecholyl, Am. J. Dis. Child. **56**:1334 (Dec.) 1938.

There was no circumoral cyanosis. The heart rate was about 300 per minute. The heart was not enlarged to percussion. Pulsations were visible over the left side of the chest. The abdomen was not distended, and the liver was not palpable.

Examination of the blood showed 11.5 Gm. of hemoglobin, 3,790,000 red blood cells and 9,800 white blood cells, with 60 small lymphocytes and 40 polymorphonuclear leukocytes. Urinalysis showed 40 to 50 white blood cells per high power field, which cleared two days later. The electrocardiogram showed a rate of 330 per minute. No P wave was seen; the QRS interval was 0.04 second, and the tracing was interpreted as probably indicative of supraventricular tachycardia. Roentgenologic examination showed that the lungs had cleared since the previous admission. The heart was greatly enlarged, with no deviation or compression of

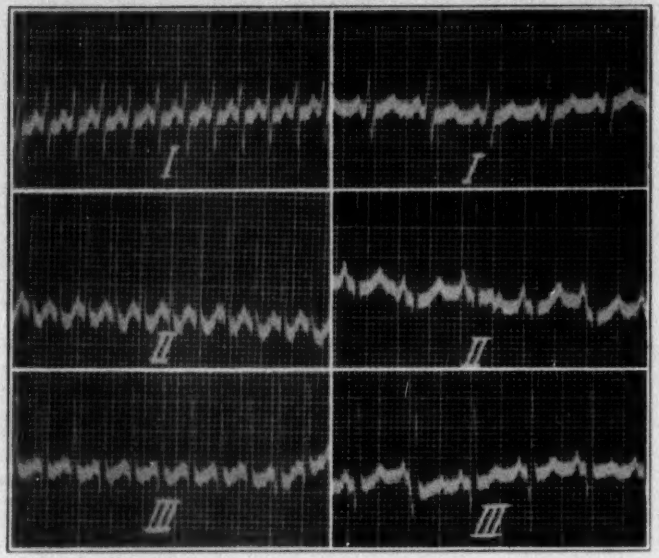

Fig. 1.—Electrocardiograms made during first attack of tachycardia (left) and after recovery from second attack of tachycardia (right).

the trachea. The impression of the examiner was generalized cardiac enlargement or dilatation, with no evidence of active pulmonary disease.

Course in Hospital.—The baby was given oxygen, 3 liters per minute, and seemed comfortable despite the continued tachycardia. The formula was taken fairly well. There was no decrease in heart rate in response to pressure over the eyeballs, carotid sinus or liver. Administration of 10 drops of tincture of digitalis U. S. P. every six hours was begun.

The second day in the hospital the formula was refused or taken slowly. The oxygen given was increased to 6 liters per minute. The face seemed puffy and the abdomen was distended. The baby appeared tired and moaned in her sleep. The temperature was approximately 100 F. (rectum). Administration of penicillin was started, 50,000 units intramuscularly every three hours, because of the pyuria.

On the third day in the hospital the patient appeared no better. The dosage of digitalis was increased to 15 drops every four hours. The temperature spiked to 103.6 F., and the baby had a weak cry and was pale and listless. The temperature came down after administration of acetylsalicylic acid, tepid sponges and cooling enemas. The baby seemed exhausted. The respirations were shallow and labored, with a faint moaning with each breath. The color became mottled. Hypodermoclyses were given to maintain fluid balance.

At 6:30 a.m. of the fourth day the baby was cyanotic and her general condition was poor. The legs were stiff with a tallow-like hardness. The pupils were

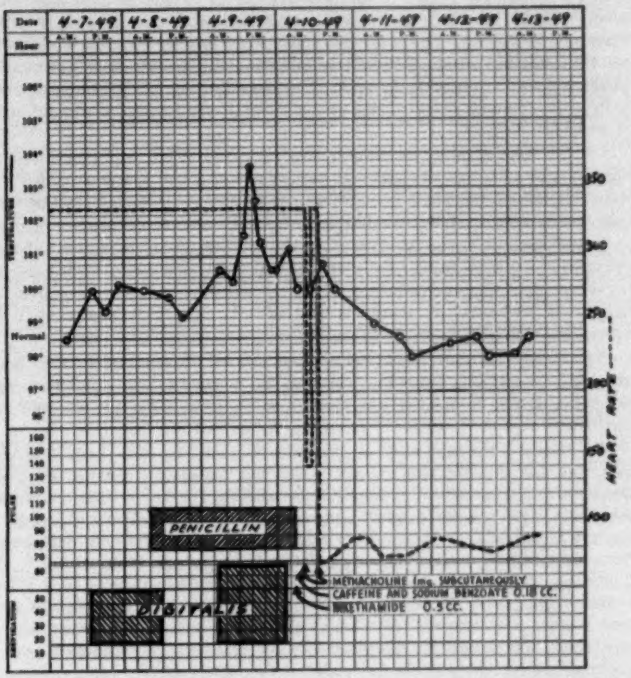

Fig. 2.—Chart showing the variations in temperature (solid line), heart rate (broken line) and medication used (shaded areas and arrows) in the hospital during the infant's first attack of tachycardia.

dilated and there were groaning respirations. All other medication was discontinued. The baby was given 3 minims (0.18 cc.) of caffeine and sodium benzoate U. S. P. intramuscularly at 6:45 and 0.5 cc. of nikethamide at 7 a.m. At 8:30, 1 mg. of methacholine chloride was given subcutaneously. The baby had a slight flush and the heart rate after two minutes dropped to 140 per minute. Three ounces (89 cc.) of formula was taken at 10 a.m.; the baby appeared hungry and 3 more ounces was taken at 10:30. At 11:45 the baby was in distress again, with mottled color and the heart rate at approximately 350 per minute. Another dose of 1 mg.

of methacholine chloride was given at 12:20 p.m., with another slight flush, and the heart rate abruptly dropped to 70 per minute. The formula was again well taken and respirations were slower and less labored. Bowel movements were normal. Administration of oxygen was discontinued the following day. The heart rate varied from 70 to 100 per minute. The baby did well for three days without medication and was discharged to the mother's care.

One week after her discharge from the hospital the baby weighed 9 pounds 12 ounces (4,423 Gm.) and administration of 10 minims (0.61 Gm.) of tincture of digitalis twice daily was started. Fluoroscopy one month later showed a normal-sized heart, and the dosage of digitalis was cut to 10 minims once daily. One month later the baby had just recovered from chickenpox and weighed 14 pounds 7 ounces (6,549 Gm.). The heart rate was 120 per minute. At about 6 months of age the infant had an acute respiratory infection, with a white blood cell count of 16,800, and was treated with penicillin. Five days later, on July 19, the paroxysmal tachycardia recurred and the baby was admitted to the hospital that night, again in peripheral collapse.

On this admission to the hospital the baby had rapid respirations (30 per minute) and cold feet and appeared pale. All soft tissue spaces retracted with each respiration, and there were visible pulsations of the rapidly beating heart (too fast to count). Otherwise the baby did not seem in distress.

Examination of the blood showed 12 Gm. of hemoglobin, 4,580,000 red blood cells and 11,300 white blood cells, with a normal differential count. Urinalysis gave normal results. The electrocardiogram on the day after her admission, when the tachycardia had subsided, showed a rate of 154. The P-R interval was 0.08 second and the QRS interval 0.05 second.

Treatment with tincture of digitalis was started, 15 drops every four hours, and within twenty-four hours the heart rate had dropped to 160. After forty-eight hours the dosage of digitalis was changed to 10 drops daily, and the baby was discharged from the hospital the following day on that dosage.

On August 1 the baby weighed 15 pounds 6½ ounces (6,988 Gm.). The heart rate was 120, and the baby seemed well. The amount of digitalis given was decreased to 8 drops daily. On August 9 the infant had moderately severe asthmatic bronchitis, with a recurrence of tachycardia, which subsided after 15 drops of tincture of digitalis was given every four hours for two days. On September 2 the weight was 16 pounds 12 ounces (7,598 Gm.) and the heart rate 120. On September 20 there was another attack of tachycardia two to three days after a common cold. With the administration of 20 drops of tincture of digitalis every four hours and 1 teaspoon (4 to 5 cc.) of elixir of phenobarbital every three to four hours, the tachycardia disappeared by the next day. She was then given 10 drops of tincture of digitalis twice daily. On October 3 the baby weighed 17 pounds 12 ounces (8,051 Gm.) and the digitalis dosage was changed to 15 drops daily. On October 17, with a mild asthmatic bronchitis, the baby had another brief attack of tachycardia, which subsided on administration of 20 drops of tincture of digitalis every four hours. Since then she has received 15 drops of tincture of digitalis twice daily, with no further difficulty.

COMMENT

The history of this baby demonstrates that paroxysmal supraventricular tachycardia may be abolished by various methods. Treatment with methacholine is obviously the most dramatic. That it is not

too dangerous is shown by Wright's case in which accidentally a dose of 100 mg. was given to an 8 year old child with no untoward effects.

According to Goodman and Gilman,[2] adequate doses of methacholine have certain cardiovascular actions. The peripheral vessels dilate, the heart slows, and the blood pressure falls. The coronary arteries primarily show dilatation, followed by constriction. This action is similar to that of acetylcholine, as are also the other pharmacologic properties of methacholine, except that it is more stable and lacks the nicotinic effects of acetylcholine on the autonomic ganglions. The stability of methacholine is significant when routes of administration in infants are considered, the subcutaneous method being much easier.

Small doses of atropine completely block the action of both acetylcholine and methacholine. The side actions of methacholine are disagreeable and include flushing, a feeling of warmth then of cold, sweating, salivation, lacrimation and palpitation. Starr reported that massage of the site of injection and alternate pressure on the carotid sinuses enhanced the action of methacholine in adults. The side actions were only temporary and a small price to pay. The authors are of the opinion that methacholine is of use only therapeutically and not prophylactically in the treatment of paroxysmal tachycardia. Digitalis seems to be the drug of choice for prophylaxis, and adequate amounts should be given.

SUMMARY

The treatment of paroxysmal supraventricular tachycardia is reviewed. A case is presented of a 10 week old infant in whom pressure on the carotid sinus, eyeballs and liver and digitalization failed; the infant seemed near death and responded dramatically to treatment with methacholine chloride. Later less severe attacks were abolished by digitalization and sedation. We believe this is the first time such a case has been reported of an infant.

Methacholine has a place in the treatment of paroxysmal supraventricular tachycardia in infants, especially when other methods seem to have failed. Atropine in small doses will block all cardiovascular actions of methacholine and should be on hand at its administration. Digitalis in adequate amounts should be given prophylactically for three months or longer following an attack of tachycardia.

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BRONCHIAL CHANGES IN EXPERIMENTALLY INDUCED CYSTIC DEGENERATION OF THE PANCREAS

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IN A RECENT report on the induction of cyst formation and consequent fibrosis in the pancreas [1] it was said that in the lungs various changes, such as hemorrhages and emphysema, occurred but squamous metaplasia or other bronchial changes were absent. Since the presentation of that study, several new series of similar experiments have been carried out and their results, together with those seen on reexamination of the original preparations, revealed data that made us revise this previous statement, especially since bronchial changes were also observed in animals in which the pancreatic lesion was provoked by deficient diets.

MATERIAL AND METHODS

Seventy-one male albino rats, ranging in weight from 160 to 190 Gm. were used.

Thirty-five animals were fed a well balanced stock diet with a liberal supplement of water-soluble vitamins and cod liver oil with added vitamin A. The amount of neither food nor water was restricted. Carbon tetrachloride, 0.07 Gm. per each 100 Gm. of body weight, was administered to the animals by subcutaneous injection every day.

Eight rats were fed a diet in which yeast, and 6 another one in which glue, formed the only source of protein. The exact composition of the diets (nos. 1 and 5, respectively) was reported in another paper.[2] Both these groups were also liberally supplied with various vitamins.

Twelve rats served as controls. Six of them were fed the same stock diet as the animals receiving carbon tetrachloride and 6 the yeast diet supplemented with 0.5 Gm. of methionine a day.[3]

Prof. J. Baló assisted in the microscopic diagnosis.

From the First Department of Pediatrics and the Institute for Experimental Medicine of the Hungarian Petrus Pázmány University.

1. Véghelyi, P. V.; Kemény, T. T., and Sós, J.: Cystic Change of the Pancreas: Its Experimental Production, Am. J. Dis. Child. **79**:65 (Jan.) 1950.

2. Véghelyi, P. V.; Kemény, T. T.; Pozsonyi, J., and Sós, J.: Dietary Lesion of the Pancreas, Am. J. Dis. Child. **79**:658 (April) 1950.

3. The methionine used in the experiments was supplied by Wyeth, Incorporated, Philadelphia.

The rats were killed by sudden severing of the abdominal aorta at different intervals, ranging from seven to one hundred and forty days.

The tissues were fixed in Bouin's fluid and embedded in celloidin or paraffin, with clearing in cedar oil. The sections stained with iron hematoxylin and eosin or Hornowsky's stain for elastic fibers and Van Gieson's triple stain.

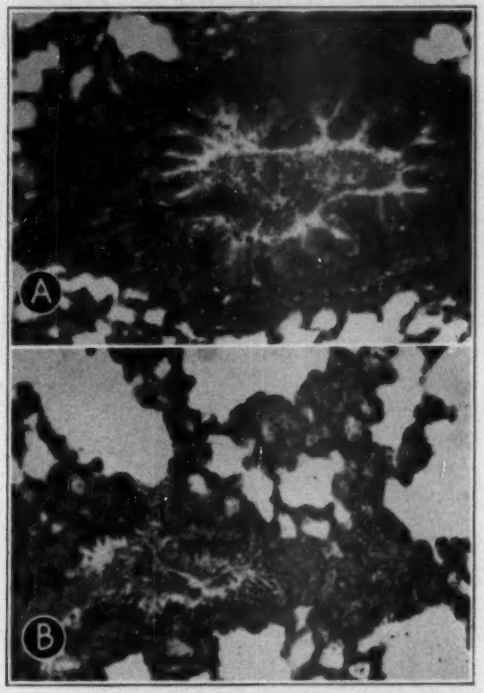

Fig. 1.—*A*, photomicrograph from lung of rat killed on thirtieth day of carbon tetrachloride poisoning, showing grave chronic peribronchitis and normal epithelium. Hematoxylin and eosin stain; Zeiss apochromatic lens, 16 mm.; 9 × compensating eyepiece. *B*, photomicrograph from lung of rat killed on fortieth day of carbon tetrachloride poisoning, showing serious chronic peribronchitis embracing adjacent parts of the lung, dilatation of bronchus and flattening of epithelium. Hematoxylin and eosin stain; Zeiss apochromatic lens, 16 mm.; 5 × compensating eyepiece.

RESULTS

None of the control animals showed bronchial changes.

Bronchiectasis, or its preliminary stages, i. e., peribronchitis and destruction of the elastic fibers and muscle layer of the bronchial wall, was present in all animals but 1 treated with carbon tetrachloride for

Fig. 2.—Photomicrograph of lung from rat killed on fiftieth day of carbon tetrachloride poisoning, showing destruction of bronchial wall by lymphocytic infiltration. Note wide gap in muscle layer in right lower quadrant, flattening of epithelium above and at left of breach and signs of beginning fibrosis. Hematoxylin and eosin stain; Zeiss apochromatic lens, 16 mm.; 9 × compensating eyepiece.

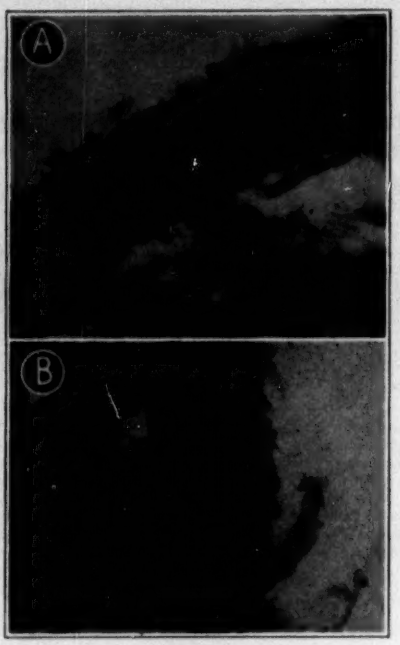

Fig. 3.—*A*, photomicrograph of lung from normal rat, showing elastic fibers of bronchial wall. Note wavy interwoven structure. Hornowsky-Van Gieson stain; Zeiss apochromatic lens, 4.3 mm.; 9 × compensating eyepiece. *B*, photomicrograph of lung from rat killed on twenty-fifth day of carbon tetrachloride poisoning. Note that the elastic wall is still normal. Hornowsky-Van Gieson stain; Zeiss apochromatic lens, 4.3 mm.; 9 × compensating eyepiece.

more than twenty-four days, in 1 from the group fed yeast and in 3 from that fed glue.

The evolution of the process could be followed precisely in the animals subjected to carbon tetrachloride poisoning. The most conspicuous change, setting in after about the thirtieth day, was severe peribronchitis affecting chiefly the medium-sized bronchi (fig. 1 *A*). The character of the inflammation was never acute, the infiltration consisting exclusively of lymphoid elements. At first, the lumens might be free but later on some of the medium-sized bronchi became obstructed by a mucinous material containing epithelial cells. With

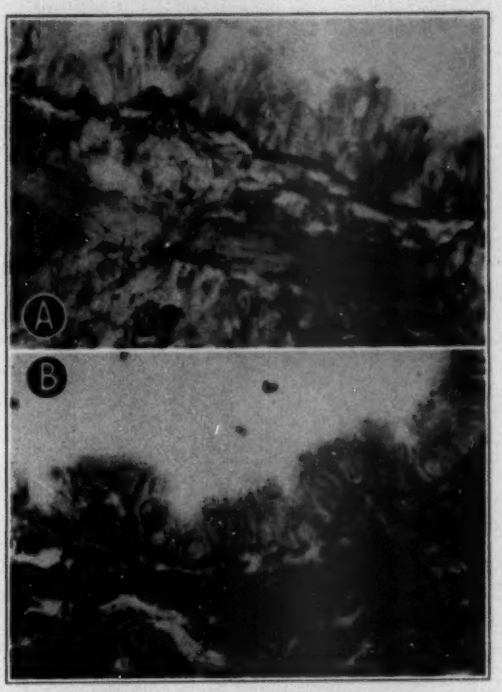

Fig. 4.—*A*, photomicrograph from lung of rat killed on thirty-fifth day of carbon tetrachloride poisoning, showing elastic fibers of bronchial wall fused into a single thick, straight line. Hornowsky-Van Gieson stain; Zeiss apochromatic lens, 4.3 mm.; 9 × compensating eyepiece. *B*, photomicrograph from lung of rat killed on fiftieth day of carbon tetrachloride poisoning, showing remnants of elastic fibers of bronchial wall broken up into rodlike formations with no structure. Note free lumen, absence of inflammatory changes and normal epithelium. Hornowsky-Van Gieson stain; Zeiss apochromatic lens, 4.3 mm.; 9 × compensating eyepiece.

time the infiltration grew more extensive, embracing large areas around the bronchus (fig. 1 *B*). Beginning formation of connective tissue as a sign of the consequent fibrosis became apparent after the sixth week, at which time the infiltration broke through the bronchial wall. The original structure of the latter was in many respects hardly recognizable and wide breaches appeared in the dissolved ring of smooth muscle (fig. 2). The epithelium of the affected bronchi suffered less, but in

Fig. 5.—*A*, photomicrograph of lung from rat killed on sixtieth day of carbon tetrachloride poisoning, showing minute points remaining from elastic ring of bronchial wall. Hornowsky-Van Gieson stain; Zeiss apochromatic lens, 4.3 mm.; 9 × compensating eyepiece. *B*, photomicrograph of lung from rat killed on fiftieth day of carbon tetrachloride poisoning, showing destruction of elastic system of bronchus (right), with elastic system of artery unaffected (left). Hornowsky-Van Gieson stain; Zeiss apochromatic lens, 4.3 mm.; 9 × compensating eyepiece.

many places a transformation into flat undifferentiated epithelium was seen.

The elastic system of the bronchi, which in normal rats consists of a structure of interwoven wavy filaments surrounding the whole

circumference in an uninterrupted line (fig. 3*A*), remained more or less intact for about twenty-five days (fig. 3*B*). It was shortly after this period that the system lost its wavy and interwoven character and

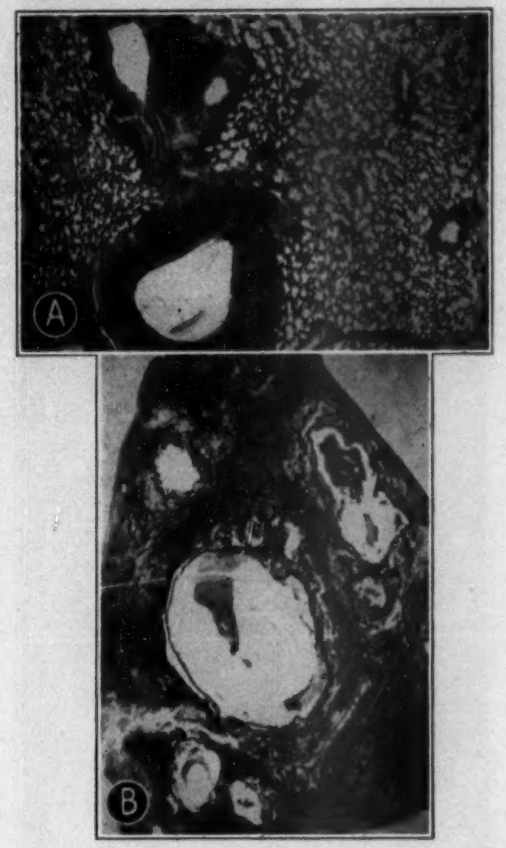

Fig. 6.—*A*, photomicrograph from lung of rat killed on sixty-fifth day of carbon tetrachloride poisoning, showing peribronchitis and dilatation of bronchioles and alveolar passages. Hematoxylin and eosin stain; Zeiss planar lens, 50 mm.; 9 × compensating eyepiece. *B*, section through lung from rat killed on the one hundred and fortieth day of carbon tetrachloride poisoning, showing cystlike multiple bronchiectases in fibrotic lung. Hematoxylin and eosin stain; Zeiss planar lens, 50 mm.; 3 × compensating eyepiece.

it became impossible to differentiate between the individual filaments, as they had fused into a single thick, straight line (fig. 4*A*). This line

Fig. 7.—Photomicrograph from lung of rat killed on eighty-fifth day of glue diet, showing peribronchitis and dilatation of bronchioles and alveolar passages. Compare with figure 6*A*. Hematoxylin and eosin stain; Zeiss planar lens, 50 mm.; 9 × compensating eyepiece.

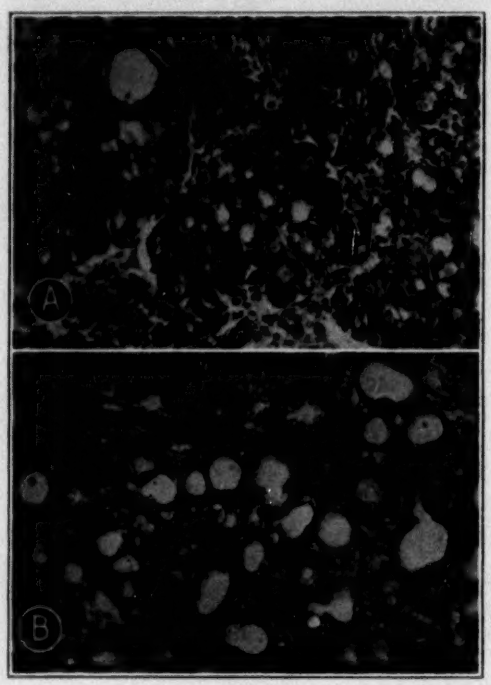

Fig. 8.—*A*, photomicrograph of pancreas from same rat as in figure 6*A*, showing shrunken lobule with cystlike dilatation of acini with fibrosis. Hematoxylin and eosin stain; Zeiss apochromatic lens, 8 mm.; 9 × compensating eyepiece. *B*, photomicrograph from same rat as in figure 7, showing dilatation of acini with fibrosis. Mallory's stain; Zeiss apochromatic lens, 8 mm.; 9 × compensating eyepiece.

soon broke up into rodlike longitudinal formations with no visible structure and no connection between the single particles (fig. 4*B*). After the fifty-fifth day only wholly unconnected minute points survived from the elastic ring, presenting the well known picture of complete dissolution (fig. 5*A*). The process was entirely confined to the elastic system of the bronchi; that of the blood vessels remained perfectly intact (fig. 5*B*).

As a result of the process, besides consolidating peribronchitis, pronounced dilatation of the bronchi, bronchioles and alveolar passages and emphysema were seen in every animal killed at about the ninth or tenth week (fig. 6*A*). As a last stage, widely dilated bronchi surrounded by fibrous tissue occupied most parts of the lung by the twentieth week (fig. 6*B*). The parenchyma of the lungs did not show inflammatory changes except in 1 rat that died with pneumonia. Hemorrhages or infarcts were present in no more than 3 animals.

The same peribronchial process occurred in several animals fed deficient diets, but in them involvement of the elastic tissue was much slighter. However, there was little difference in the result, as in 2 animals, of which 1 died and the other was killed in the thirteenth week, the lungs presented precisely the same picture of peribronchitis with dilatation of bronchi, bronchioles and alveolar passages (fig. 7) as those of the rats treated with carbon tetrachloride.

In the pancreas, dilatation of acini leading to cyst formation associated with fibrosis was observed in all three groups, as already reported in our previous studies.[4] However, the photomicrographs of the pancreases of 2 animals, 1 from the group given carbon tetrachloride and 1 from the group given the glue diet, the lungs of both of which are shown, are also reproduced for the sake of comparison (fig. 8).

COMMENT

The experiments clearly demonstrated that, together with cystic degeneration and fibrosis of the pancreas, chronic peribronchitis and fibrosis of the lungs, leading to extensive bronchiectasis, may be produced at will by chronic poisoning with carbon tetrachloride. In the pathogenesis of the pulmonary lesion, however, many points remain obscure. As the major part of halogenated hydrocarbons is eliminated through the lungs, one would tend to ascribe the bronchial changes to some local irritative effect of carbon tetrachloride. However, apart from the fact that similar bronchial lesions could, although less frequently, be observed also in animals which had been fed deficient diets but which had been given no poison whatever, there remain several phenomena which seem to contradict that assumption. First of all, if

4. Footnotes 1 and 2.

the changes observed were due to the irritative property of some substance, then the tissue to suffer primarily would be the parenchyma of the lungs and the mucous membrane of the bronchi. Still, apart from secondary emphysema and dilatation, the alveolar system remained normal throughout the process and no inflammation, ulcers or other changes could be observed in the mucous membranes before at least partial destruction of the bronchial wall from without was seen. Further, destruction of the elastic fibers seems to be a phenomenon quite independent from the peribronchial infiltration, as total decay of the elastic system may occur in bronchi bearing no sign of inflammation (see figs. 4 *B* and 5 *A*). Then, at the beginning, the process seems to be confined to bronchi above a certain size, and it is only much later that smaller branches of the system also become involved. Neither does obstruction seem to play a deceptive role. If present, it is usually partial, but in only the lungs displaying the gravest lesions do the lumens remain free (figs. 6 *A*, 6 *B* and 7).

In spite of problems concerning both the exact pathogenesis of the lesions induced and their somewhat different development, it seems that the principal changes characterizing the fibrocystic disease of the pancreas, viz., formation of cysts and fibrosis in the pancreas associated with bronchiectases, may be serially induced by chronic poisoning with carbon tetrachloride and incidentally also by deficient diets. The data at our disposal are far from sufficient to permit conclusions concerning the pathogenesis of the fibrocystic disease of the pancreas, but they seem to indicate the need for a thorough examination of the factors involved.

SUMMARY

Extensive bronchiectasis following peribronchitis, destruction of the building elements of the bronchial wall and consequent dilatation of bronchioles and alveolar passages, together with cystic degeneration and fibrosis in the pancreas, were serially produced in rats by means of chronic poisoning with carbon tetrachloride and incidentally also by deficient diets.

The findings seem to indicate the necessity for thorough investigation of the factors involved in the pathogenesis of cystic fibrosis of the pancreas.

Case Reports

ATROPINE INTOXICATION IN INFANCY

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ROCHESTER, N. Y.

ATROPINE, widely used for the treatment of colic in infancy, has been generally considered to be a safe drug.[1] However, the frequent occurrence of certain undesirable side effects, even when small doses are employed, has caused many physicians to refrain from using this medicament.

The purpose of this paper is to describe in detail a case of atropine poisoning with recovery in a 7 week old infant as a result of ingestion of more than 40 mg. of the drug within a twenty-four hour period. In addition, the toxicologic and diagnostic features are reviewed, and the therapeutic management of the present case is discussed.

REPORT OF A CASE

W. W., a 7 week old white male infant, was admitted to the Strong Memorial Hospital Oct. 24, 1948 at 12:55 a. m. with intermittent fever of approximately twenty-four hours' duration and convulsions beginning about seven hours before his admission. Pregnancy, delivery and neonatal history were uneventful. The infant was totally breast fed. Adequate vitamin supplements were given in a multivitamin preparation (vi-penta®), five drops daily. Three weeks prior to his admission, intermittent colicky pain was observed. At about the same time he began to regurgitate small amounts of gastric contents shortly after feedings. This was treated unsuccessfully with calcium hydroxide solution (lime water) and boiled water. The colicky distress increased in severity and duration until two days before his admission, when crying was almost continuous between feedings. Since an older sibling had been relieved of colicky symptoms at the age of 6 months by the substitution of a hypoallergenic soy preparation (mull-soy®) for breast feeding, syrup of thephorin®[2] was prescribed at that time, ¼ to ½ teaspoon (1 to 3 cc.) before each feeding. The prescription was telephoned to a pharmacist who misunderstood the physician's instructions and compounded a 1 per cent (!) solution of atropine sulfate U. S. P. to be given according to these instructions.

On October 22 at 7 p. m. the first dose of ½ teaspoon was given in a small amount of water and was entirely retained.

At 10 p. m. ¼ teaspoon was administered similarly, although part of this dose, probably less than half, was spit out. The child was warm and flushed and seemed to be having abdominal pain. He had not voided in three hours.

On October 23 doses of ¼ teaspoon were given at 2 a. m., 10 a. m., 2 p. m. and 6 p. m. A portion of each of these doses was spit out. It is conservatively esti-

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From the Department of Pediatrics, University of Rochester School of Medicine and Dentistry, and the Strong Memorial and Rochester Municipal Hospitals.

1. White, P. J.: Atropine Fever in Early Infancy, Am. J. Dis. Child. **37**:745 (April) 1929.

2. Thephorin® is a commercial preparation of phenindamine, an antihistaminic compound, which is 2-methyl-9-phenyl-2, 3, 4, 9 tetrahydro-1-pyridindene hydrogen tartrate. Syrup of thephorin® is a 0.2 per cent solution (10 mg. per 5 cc.).

mated, however, that half or more of the amounts offered was retained. The appetite had remained good until 6 p. m. on this date. Shortly thereafter, the child was found with his extremities stiffened, his arms tightly flexed and legs extended.

From 6 to 10 p. m. the child cried incessantly. At 9 p. m. he was offered and accepted 2 ounces (60 cc.) of tea and 3 ounces (90 cc.) of water.

A dose of ¼ teaspoon of the atropine sulfate solution given at 10 p. m. was retained. The temperature was 104 F. The face was hot, dry and flushed. The eyes were staring and rolled up and back. The child was stiff, trembling and unresponsive. Respirations were rapid and shallow. The mouth was dry. Tepid baths quieted him temporarily.

At 12 midnight the rectal temperature was 105 F. A warm, soapy enema was given which was productive of small amounts of stool and mucus. A pediatrician was called, who sent the patient to the hospital with a presumptive diagnosis of atropine poisoning, although the pharmacist's error was not known to him at that time.

Cursory examination at the time of the patient's admission to the hospital revealed a severely, acutely ill infant, who was unresponsive and having a generalized tetanic convulsion. The eyes were rolled upward, with the pupils widely dilated and fixed. The rectal temperature was 101 F. The pulse rate was over 200, and the respirations were rapid and shallow. The bladder was palpable at the level of the umbilicus. The oral mucous membranes, conjunctivas and corneas were completely dry.

Therapy was instituted at once (12:55 a. m., October 24). Thirty cubic centimeters of milk was removed from the stomach, which was then lavaged with 500 cc. of warm tap water. Pilocarpine nitrate U. S. P., 0.001 Gm., was injected subcutaneously. Thiopental sodium U. S. P. (pentothal sodium®) was injected slowly by vein to control the convulsion. One cubic centimeter (0.025 Gm.) was required, but respirations abruptly ceased. Immediate artificial respiration and the subcutaneous injection of caffeine and sodium benzoate U. S. P., 0.5 cc. (0.125 Gm.), restored spontaneous breathing within two minutes. Generalized convulsions recurred, which were again controlled by the slow intravenous injection of 1 cc. of thiopental sodium. Respirations were unaffected. Continuous administration of oxygen by oxadome® (a type of oxygen tent) was begun, with immediate improvement in the patient's dusky color. Respirations soon became irregular, however, but improved following the subcutaneous injection of 0.5 cc. of caffeine and sodium benzoate. The patient was catheterized, and a large amount of clear, light-colored urine was obtained by gentle pressure on the abdomen. The catheter was allowed to remain in place. A recurrence of respiratory irregularity was treated successfully by the subcutaneous injection of 1 cc. (0.375 Gm.) of nikethamide. One drop of a 0.5 per cent solution of pilocarpine nitrate was instilled into each eye.

A generalized clonic convulsion occurred at 1:45 a. m. and was controlled by the subcutaneous injection of 1 cc. of thiopental sodium. The pulse was regular at a rate of 120 per minute. Respirations were regular and of moderate depth. The color was good, and the patient seemed much improved. Spontaneous movements of the extremities were noted for the first time. The patient passed flatus and began to cry. The subcutaneous injection of penicillin, 20,000 units every six hours, was begun to guard against possible secondary infection.

At 2:25 a. m. a right-sided convulsion was controlled by the subcutaneous injection of 0.5 cc. of thiopental sodium. The skin was still warm and dry, although the flush was less pronounced. The right pupil was smaller than the left, presumably a pilocarpine effect. Corneas, conjunctivas, nasal mucous membrane, lips and

mouth were dry. Respirations were rapid and shallow at a rate of 88 per minute. The heart rate was 140 per minute and the sounds were of good quality. The abdomen was tense and distended. The bladder was palpable at the umbilicus. The deep tendon reflexes were hyperactive.

Predominantly right-sided convulsions recurred repeatedly at about half-hour intervals. Just enough thiopental sodium was injected to control the seizures. The child slept quietly between attacks. Pilocarpine ophthalmic ointment, 1 per cent, was applied to the conjunctivas. Eighty cubic centimeters of 5 per cent dextrose in Ringer's solution was injected intravenously. At about 5 a. m. the oral mucous membranes were moist and tenacious mucus had begun to collect in the upper respiratory passages, requiring gentle suction with a soft rubber catheter to maintain an opening. At 5:30 a. m. a semisolid, brown stool was passed spontaneously. By 7 a. m. the child was sleeping quietly; the pulse was 110 per minute and regular, and the skin was paler. A final generalized convulsion occurred at 9 a. m., which was treated successfully as before.

Further use of sedatives was not necessary. During the day the child slept quietly and was not disturbed. Respirations, pulse and temperature gradually returned to normal. By 8:30 p. m. he was awake and crying and eagerly took 2 ounces of 5 per cent dextrose in isotonic sodium chloride solution by mouth. Fluids were given by mouth and subcutaneously to correct moderate dehydration. The catheter was removed, and he was subsequently able to void spontaneously. By the following morning he accepted full feedings and was completely without symptoms except for cycloplegia, which disappeared later in the day.

On October 25 the red blood cell count was 4,000,000, the hemoglobin concentration, 11 Gm. and the white blood cell count, 12,000, with 53 per cent neutrophils. The urine was entirely normal except for a trace of albumin. Urine obtained from the indwelling catheter on the night of admission failed to produce mydriasis when instilled into the conjunctiva of a cat.

The remainder of the hospital course was uneventful, and the patient was discharged on the third day from the hospital. It is of interest that during the several months since his discharge he has been completely free of colicky distress. Growth and development have progressed normally, and there have been no sequelae.

EFFECTS AND TREATMENT OF ATROPINE POISONING

The belladonna alkaloids and related synthetic drugs are widely employed in treating infants, primarily as spasmolytics and as mydriatics. White[1] noted that toxic symptoms most commonly occurred following the instillation of two drops of a 1:1,000 solution (0.2 mg.) into the conjunctiva. Fatalities[3] are rare, however, despite the frequency of toxic manifestations.

Symptoms and signs of intoxication are seen frequently following the administration of atropine or belladonna. They are less common with some of the synthetic derivatives such as atropine methylnitrate (metropine®; eumydrin®), homatropine methylbromide N. F. (novatrin®) or amprotropine phosphate N. N. R. (syntropan®). Toxic signs fall into two groups: (*a*) those resulting from the effects of the drug on the central nervous system and (*b*) those resulting from paralysis of structures innervated by postganglionic parasympathetic nerves.

3. (*a*) Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics: A Textbook of Pharmacology, Toxicology and Therapeutics for Physicians and Medical Students, New York, The Macmillan Company, 1941. (*b*) Morton, H. G.: Atropine Intoxication: Its Manifestations in Infants and Children, J. Pediat. **14**:755, 1939.

Central effects [4] of some synthetic compounds, particularly the methyl atropines, are minimal; peripheral actions are retained but may be weaker. The primary effect of atropine on the central nervous system is acute stimulation, which may be present to a notable degree even though the dose has been small. Fever, which may be alarmingly high, restlessness, convulsions and rapid respirations are frequent in infants. The skin is hot, dry and flushed. A rash, often scarlatiniform, may appear over the face, neck and upper portion of the trunk and may even be followed by desquamation. Nausea and vomiting are not uncommon. In addition, older persons may become disoriented, mildly delirious, weak and poorly coordinated. The mechanism of this excitation of the central nervous system is not clear. Atropine [4b] stimulates the medulla and higher cerebral centers probably by direct irritant action rather than by removal of inhibition. This effect on the central nervous system may be the reason for the extreme toxicity of atropine for human beings compared with other animals, notably rodents. However, all parts of the brain are not stimulated, since atropine,[5a] apparently by a primary depression of certain central motor mechanisms, has a specific sedative action on the tremor and rigidity of parkinsonism. The phase of central excitation is often followed by one of severe depression, which may result in coma, circulatory collapse, respiratory failure and death.

The symptoms and signs resulting from paralysis of structures innervated by postganglionic cholinergic nerves provide important diagnostic criteria. The pupils are widely dilated and fixed. The tongue, mucous membrances and conjunctivas are dry. Tachycardia and abdominal distention may occur, and the bladder may be palpable above the pubis. Older persons complain of extreme thirst, difficulty in swallowing and talking, photophobia, blurred vision, palpitation, urgency, difficult micturition and pronounced general discomfort.

A diagnosis of atropine poisoning is ordinarily not difficult if the possibility is kept in mind. It may be confused with scarlet fever when the rash, fever, tachycardia and delirium are prominent symptoms. When the diagnosis is in doubt, the administration of a small amount (3 to 10 mg.) of acetylmethylcholine [5] will result in salivation, sweating, lacrimation and intestinal hyperactivity only in the absence of an atropine effect. A small amount of urine may also be instilled into the conjunctiva of a cat. Mydriasis [6] will result if 0.0003 Gm. of atropine is present. Acute alcoholic and schizophrenic psychoses must also be differentiated in older patients.

Although the fatal dose [3a] of atropine for infants is stated as about 10 mg., survival is certainly possible following much larger doses. An adult [7] has recovered after the ingestion of 1 Gm. of atropine sulfate, a dose which is approximately ten times the lethal dose [3a] usually cited. Comroe's well known patient [8] recov-

4. (*a*) Goodman and Gilman.[3a] (*b*) Stoll, H. C.: Pharmacodynamic Considerations of Atropine and Related Compounds, Am. J. M. Sc. **215**:577, 1948.

5. Anderson, J. A., in Nelson, W. E.: Mitchell-Nelson Textbook of Pediatrics, ed. 4, Philadelphia, W. B. Saunders Company, 1945.

6. (*a*) Goodman and Gilman.[3a] (*b*) Pilcher, J. D.: Atropine Tolerance in Infants and Children: The Negative Action of the Serum of Tolerant Subjects, J. Pharmacol. & Exper. Therap. **52**:196, 1934.

7. Alexander, E.; Morris, D. P., and Eslich, R. L.: Atropine Poisoning: A Case with Recovery After Ingestion of One Gram, New England J. Med. **234**:258, 1946.

8. Comroe, B. J.: Atropine Poisoning: Recovery After Ingestion of 7½ Grains of Atropine Sulphate by Mouth, J. A. M. A. **101**:446 (Aug. 5) 1933.

ered after 0.5 Gm. of the same drug had been taken. In the case under discussion, a 7 week old infant ingested and retained at least 40 mg. in twenty-four hours. The actual amount was probably closer to 70 mg. or more, since the child was offered a total of 100 mg., several doses of which were entirely retained. Recovery has been complete.

Lewis and his associates[9] injected 1.2 to 6.5 mg. of atropine sulfate hypodermically and intravenously in adults without observing important toxic effects.[10] Their observations indicated that as much as 6.5 mg. of atropine might be required to produce complete paralysis of the vagus. In view of these findings, Wedd[10] suggested that the accepted dose of atropine may be too small for optimum effect and that minor toxic reactions of the peripheral type are of no consequence beyond temporary discomfort.

Atropine,[4b] rapidly absorbed from the gastrointestinal tract, disappears from the peripheral blood within a short interval. About one third of the ingested dose[4b] may be recovered from the urine, and the remainder is thought to be hydrolyzed in the liver. Traces are detectable in the milk and sweat. An esterase[11] hydrolyzing atropine, present in the serum and certain tissues of some animals, notably the rabbit, has not been demonstrated in human serum. This is true, even in the case of infants who seem to possess unusual tolerance[4b] to the effects of atropine. The mechanism for such tolerance is yet to be explained. In general, infants[4b] have fewer symptoms of central nervous system excitation, display a more pronounced sedative effect and show great variations in resistance. The infant of the present case did not seem to illustrate these differences, although his tolerance for these drugs was never studied under controlled conditions. Pilcher's observations[9b] that tolerant subjects show minimal evidence of the usual signs of atropine action, even after large doses, and that such infants sleep deeply without a preliminary period of excitation would not suggest that this patient is unusually tolerant to atropine.

Infants, and older persons as well, who suffer from atropine poisoning are a therapeutic challenge. There is no antidote which successfully counteracts both central and peripheral effects. Pilocarpine is useful in neutralizing such peripheral autonomic effects as antisialogogic action, mydriasis and others, but it does not influence the more serious central nervous system symptoms. Moreover, in large doses, pilocarpine may depress the central nervous system, an effect which might be dangerous should it coincide with the severe secondary depression of atropine poisoning. Pilocarpine was used in small doses in the present case only for the relief of peripheral symptoms.

Gastric lavage is recommended whenever it is suspected that some of the alkaloid may be present in the stomach. Strong tea or dilute tincture of iodine will precipitate the drug and both are satisfactory for this purpose. Potassium permanganate[8a] is not effective. Finely powdered charcoal may be added as an adsorbent. In the present instance, tap water alone was used. It seemed unlikely at the time of this patient's admission that large amounts of atropine were present in the stomach.

For central nervous system excitement, short-acting barbiturates, paraldehyde or chloral hydrate[8a] have been recommended. Small doses should be employed

9. Lewis, T.; Drury, A. N.; Wedd, A. M., and Iliescu, C. C.: Observations upon the Actions of Certain Drugs upon Fibrillation of the Auricles, Heart 9:207, 1922.

10. Wedd, A. M.: Personal communication to the author.

11. Pilcher.[4b] Stoll.[4b]

in order that their action may not coincide with the secondary stage of depression. Here, thiopental sodium, a short-acting barbiturate, was used successfully in repeated doses, each sufficient to control convulsions. Such doses, however, caused cessation of respirations on one occasion. The margin of safety was narrow, and one wonders whether spontaneous respirations could have been reestablished so easily had a longer-acting sedative been used. The level of excitement was quite readily controlled with this drug, with minimal risk of carryover into the anticipated dangerous stage of depression. Experience with a short-acting barbiturate in this case seems to recommend further trial for this mode of sedation in the management of the stage of excitement. A 7 week old infant received a total of 216 mg. of thiopental sodium in nine hours and suffered no ill effects.

Central nervous system stimulants must be used as vigorously as necessary when and if the stage of depression occurs. Respiratory irregularities in our patient were successfully managed by the administration of caffeine and sodium benzoate injection, oxygen, nikethamide and artificial respiration. Carbon dioxide, 5 per cent, in oxygen, 95 per cent, may be used. Ephedrine, strychnine or picrotoxin may be of value in more extreme situations.

Difficult micturition or acute urinary retention should be treated by use of the indwelling catheter until sphincter control is reestablished.

Fever can be controlled by tepid baths or sponges, alcohol sponges or ice bags.

COMMENT

The all too frequent occurrence of therapeutic accidents is illustrated again in this case. The importance of writing and carefully reading all drug orders in order books or on prescription blanks cannot be overemphasized. We are reminded too that the pharmacist's responsibility does not end when he has accomplished what he understands to be the physician's instructions. He must be certain in every case that what he compounds and labels is safe. Only the unceasing vigilance of all concerned with the dispensing of drugs will minimize the number of these tragedies and near tragedies.

Accidental belladonna poisoning occurs occasionally among older children and adults. Berries of the large fruiting shrubs, atropa belladonna, are sometimes eaten. The ingestion of rabbit or fowl fed on belladonna berries may result in poisoning. Unlooked-for toxic symptoms may follow the application of belladonna plasters to the breasts or scrotum or the use of rectal suppositories containing atropine. Patients receiving atropine medicaments, such as eye drops, some prescriptions for enuresis and medicines for spastic gastrointestinal disorders, should be observed for untoward signs. Fixed proprietary drug combinations containing belladonna alkaloids are better avoided because of lack of flexibility in adapting the amounts of the various components to individual needs.

The place of atropine in the therapeutic armamentarium of the pediatrician might well be reexamined. The pediatric applications of some of the newer synthetic drugs, such as atropine methylnitrate, homatropine methylbromide, amprotropine phosphate, adiphenine hydrochloride (trasentine®) and beta-diethylaminoethyl fluorene-9-carboxylate hydrochloride (pavatrine®) deserve further study. These agents are usually somewhat weaker than atropine in their peripheral actions, but they are considerably less toxic. Amprotropine phosphate and adiphenine hydrochloride[4a] act more selectively to relax smooth muscle directly rather than by a parasympathetic blocking effect. Undesirable side reactions are minimal. The action of pavatrine® is similar. Atropine methylnitrate, said[4b] to be fifty

times less toxic than atropine, has been used[12] with some success in the treatment of pyloric stenosis and pyloric spasm. Homatropine methylbromide and eucatropine hydrochloride[5b] are usually satisfactory mydriatic drugs. Their peripheral actions are weaker than those of atropine, but poisoning from their use in less common. Stoll[4b] recently reviewed in detail the pharmacodynamics of atropine and related compounds, chiefly atropine methylnitrate. More such studies of other drugs in this group are needed.

SUMMARY

1. A case of severe atropine intoxication with recovery in a 7 week old infant is presented.

2. The symptoms and signs of atropine intoxication are reviewed.

3. Treatment is discussed, and the use of the short-acting barbiturates is recommended for counteracting severe central nervous system excitation.

4. The position of atropine in pediatric therapeutics is challenged, and the need for further study of medicaments in this group is cited.

5. The constant danger of therapeutic accidents is reemphasized.

Dr. C. H. Falkenheim gave permission for publication of a report of this case.

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12. Stoll,[4b] Dobbs, R. H.: The Treatment of Pyloric Stenosis with Eumydrine, Lancet **1**:12, 1939.

SPLENIC PANHEMATOPENIA IN CHILDREN

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IN 1944, Doan [1] described a blood dyscrasia which in his opinion was caused by a malfunctioning spleen. He pointed out certain similarities among this so-called panhematopenia, congenital hemolytic anemia and primary thrombopenic purpura. He postulated that in primary splenic panhematopenia the spleen does not exercise selectivity for any particular element of the blood in its pathologic destructive tendency, but that it destroys all of them at an excessive rate. Recently, Doan and Wright [2] discussed this subject in more detail. In contrast to Doan's opinion, Dameshek [3] expressed his feeling that the overactive spleen inhibits the bone marrow, possibly by hormonal control. Both authors emphasized the reality of the syndrome and pointed out the benefits of splenectomy in selected cases. Because of the paucity of reports of this syndrome descriptions of 2 cases are presented.

REPORT OF CASES

CASE 1.—B. S., a white girl 11 years of age, was admitted to the North Carolina Baptist Hospital on Aug. 5, 1947, because of "spleen trouble all of her life."

The family history revealed that a paternal first cousin of the patient, a girl, died at the age of 2 to 3 years of a "blood disease" characterized by splenomegaly and severe anemia.

The mother's pregnancy was uneventful, and the patient was delivered at term. The neonatal period was not remarkable except for pallor. There was no neonatal jaundice. Development was normal.

Though pale, the patient did well until the age of 2 years, when she had "diphtheria and pneumonia." Following this, she received a transfusion because of anemia. The child remained fairly well, though pale, until she had "pneumonia" when she was 5 years old. She received transfusions and a preparation of iron and liver at that time. The parents were told that the child had a large spleen and "bad anemia." Again, she did fairly well until 8 years of age, when she had another attack of "pneumonia." After that, her condition seemed to go downhill, and she required transfusions more frequently. At that time, jaundice was noted. This varied in intensity. The urine was dark amber, but the stools were always of normal color. The child complained intermittently of abdominal

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1. Doan, C. A.: Primary Splenic Pan-Hematopenia, Proc. Central Soc. Clin. Research **17**:32-34, 1944.

2. Doan, C. A., and Wright, C. S.: Primary Congenital and Secondary Acquired Splenic Panhematopenia, Blood **1**:10-26 (Jan.) 1946.

3. Dameshek, W.: Medical Progress: Hematology, New England J. Med. **234**:829-838 (June 20) 1946.

pain and nausea. In the six months before her entry into the hospital, there were five episodes of severe jaundice, at which times she was given transfusions.

Physical examination on her admission revealed a chronically ill child with extreme pallor and icteric skin and scleras. The heart was slightly enlarged, and a grade III, blowing systolic murmur was heard over the entire precordium. The pulse rate was 92 per minute. The liver was palpable 6.5 cm. below the right costal margin and was smooth, firm and nontender. The spleen extended down to the pelvic brim and medially to the umbilicus and was hard, smooth, nontender and freely movable. Small lymph nodes were present in the inguinal, axillary and cervical areas.

The laboratory studies on her admission showed normal urine. Excretion of urobilinogen was increased, color being present in a dilution of 1:40; urobilin was detected but bile was not present. Results of studies on the blood are shown in figure 1. The total serum proteins were 6.4 Gm. per hundred cubic centimeters;

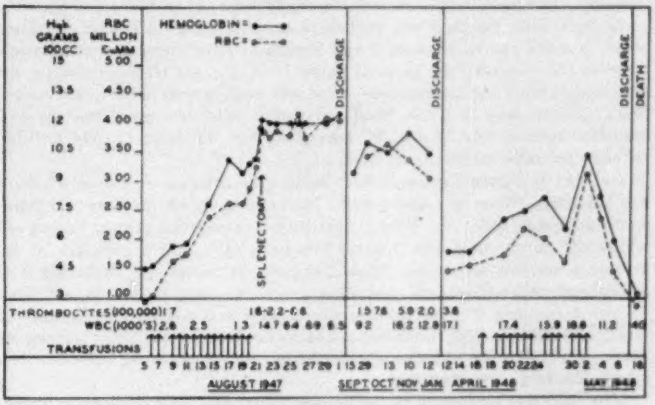

Fig. 1.—Results of studies on the blood of patient B. S. (case 1).

the van den Bergh reaction showed 4.5 mg. of bilirubin per hundred cubic centimeters, and the icterus index was 25 units. The Kahn reaction was negative; repeated stool examinations revealed no ova, parasites or cysts; tests gave strongly positive reactions for bile and negative reactions for occult blood. Fragility tests and bleeding, clotting and prothrombin times were within normal limits. A preparation of the blood exhibited no sickle cells. Fluoroscopy showed no esophageal varices, and a roentgenogram of the skull revealed no abnormality.

The patient was given repeated transfusions of packed red cells and whole blood, following which the spleen definitely decreased in size. The jaundice became less prominent. On August 12, a biopsy specimen of a lymph node showed chronic lymphadenitis. Bone marrow aspirated six days later showed generalized hyperplasia of the erythrocytic series, with a predominance of erythroblasts. Repeated transfusions failed to raise the hemoglobin concentration and red blood cell count above 10.5 Gm. and 3,210,000 per cubic millimeter, respectively. The white count varied from 1,000 to 2,000 cells per cubic millimeter. An epinephrine tolerance test was done, showing minimal decrease in

the size of the spleen, a moderate increase in the number of red cells, a definite decrease in the number of white cells and no change in hemoglobin concentration.

Though it was doubted that splenectomy would be effective, it was believed that there was no other therapy to offer, and on August 21, a transthoracic splenectomy was done. The spleen was large and dark. The pathologist's report was "generalized reticuloendothelial hyperplasia with no detectable increase in the amount of deposition of iron pigment." No further transfusions were necessary after the operation. Twenty-four hours after splenectomy the hemoglobin concentration was 12.2 Gm., the red blood cell count, 3,830,000 and the thrombocytes, 180,000 per cubic millimeter. After an uneventful postoperative course, the patient was discharged from the hospital on September 1. Figure 1 shows the results of studies on the blood at the time of her discharge. Clinical jaundice was absent and the patient felt well.

The patient was followed at frequent intervals and seemed to be doing exceptionally well until Jan. 12, 1948, when the parents noted the recurrence of jaundice. The urine was dark and the stools were of normal color.

In April 1948, the child was readmitted to the hospital because of increasing pallor, jaundice and an enlarged liver. Results of blood chemical determinations made on this admission are given in figure 1. Again, the bleeding, clotting and prothrombin times and the reactions to red cell fragility tests were within normal limits. Transfusions of whole blood and packed cells were given, but the concentration rose to only 8.5 Gm. of hemoglobin and the count to only 2,670,000 red cells per cubic millimeter of blood.

On May 1, a laparotomy was done because the presence of accessory spleens was suspected. None was found, but a biopsy specimen of the liver and retroperitoneal lymph nodes was taken. Microscopic examination showed "round cell infiltration" in the liver and "chronic lymphadenitis." The significance of the infiltration was not determined. Nine days later the patient was discharged from the hospital, still with clinical jaundice and with the liver palpable 3 cm. below the costal margin. The hemoglobin concentration was 6 Gm. and the red cell count, 1,800,000 per cubic millimeter. The patient was up and about and feeling fairly well. Since she had shown improvement with a low blood cell count previously, discharge was permitted.

The child was readmitted to the hospital seven days later, with fever, vomiting and restlessness. She had progressed satisfactorily until the day of her admission, when fever and vomiting developed. The temperature was 104.2 F. (rectally), the pulse rate, 160 to 170 per minute and the respiration, 32 per minute. She was jaundiced and extremely pale, and there was decided distention of the veins of the neck, especially on the right. A grade IV, blowing systolic murmur was heard over the entire precordium, and a gallop rhythm was present. The liver was tender and descended 7 to 8 cm. below the costal margin. Results of determinations on the blood are shown in figure 1. A transfusion of packed red cells was started and digitalization was begun. The patient died about twelve hours after her admission. Permission for autopsy was not obtained.

CASE 2.—T. R., a 9 year old white boy, was admitted to the North Carolina Baptist Hospital on Aug. 30, 1947, with the complaint of pallor and great fatigability for the previous three months.

The family history was noncontributory.

Neonatal and developmental histories were normal.

The child had been healthy until April 1947, at which time he had "pneumonia" and was treated with penicillin and sulfonamide compounds. He recovered from the illness and returned to school, but early in June 1947 pallor and

weakness were noticed. He was discovered to be anemic and was given a "tonic" and intramuscular injections of a liver preparation. There was no improvement, and on August 2 the child received four whole blood transfusions. He was discharged from the hospital two weeks later, with instructions for oral administration of liver and iron.

He failed to respond to this therapy and on August 28 had an episode of nausea and vomiting, unassociated with abdominal pain, chills or fever. A similar episode occurred on August 29. The parents believed the pallor and jaundice appeared at the same time and steadily increased without remission. No history could be obtained of the color of the urine or stools. He was referred to the North Carolina Baptist Hospital for diagnostic study.

Physical examination on his admission on August 30 revealed a rectal temperature of 100.2 F., a pulse rate of 128 per minute and a respiratory rate of 28 per minutes. The child was well developed, well nourished and unusually

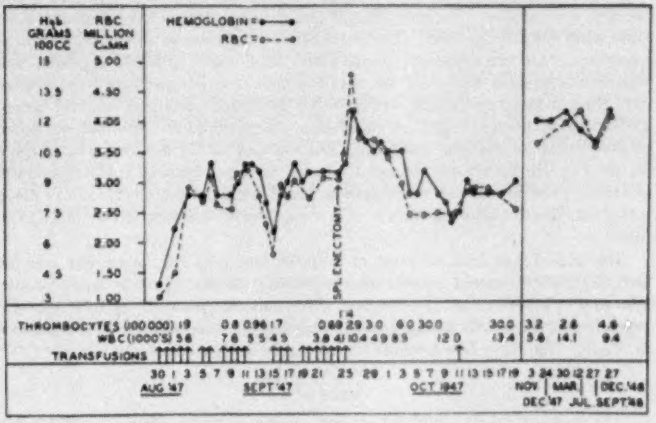

Fig. 2.—Results of studies on the blood of patient T. R. (case 2).

intelligent. The skin and scleras were moderately icteric and the mucous membranes pale. There were small, discrete inguinal and epitrochlear nodes. The heart was slightly enlarged, and a grade III, blowing systolic murmur was heard over the entire precordium. A gallop rhythm was present. The liver was palpable 5 cm. below the right costal margin, and the spleen was palpable 8 cm. below the left costal margin. Neither the liver nor the spleen was tender.

Laboratory studies on this admission showed normal urine. Excretion of urobilinogen was increased, color being visible in a dilution of 1:40, but there was no detectable bile. Figure 2 shows the results of blood studies. The van den Bergh test revealed 2 mg. of bilirubin per hundred cubic centimeters of serum. Repeated examinations of the stools failed to show ova, parasites, cysts or occult blood. Bile was present. The first Kahn reaction was reported as doubtful, but subsequent serologic tests for syphilis gave negative reactions. Red cell fragility and bleeding and clotting times, as well as prothrombin time, were all well within normal limits. Aspiration of bone marrow showed pronounced hyperplasia of the erythrocytic series.

During the first twenty-three days in the hospital, nineteen transfusions failed to raise the hemoglobin concentration above 9.5 Gm. or the red blood cell count above 3,150,000 per cubic millimeter. There was no definite change in the size of the spleen. An epinephrine tolerance test was done. At that time, the spleen decreased decidedly in size, the white and the red blood cell counts rose moderately and the hemoglobin concentration rose minimally.

On September 25, a transthoracic splenectomy was done. The spleen weighed 402 Gm. and its appearance was reported as being "compatible with that found in hemolytic anemia." Twenty-four hours after the operation the hemoglobin concentration was 12.5 Gm., the red blood cell count, 4,750,000 and the thrombocyte count, 290,000, per cubic millimeter.

The postoperative course was uneventful except for mild, unexplained fever for twelve days. On the twelfth postoperative day the patient's temperature rose to 104.8 F. and remained elevated for three days. Repeated blood smears at these times failed to show the presence of malarial parasites; repeated blood cultures were sterile. The only clinical change was slight enlargement and moderate tenderness of the liver. The possibility of homologous serum hepatitis was considered. On the sixteenth postoperative day, giant urticaria appeared and was present to some degree for the next five days. By the sixteenth postoperative day, the red blood cell count was 2,200,000 per cubic millimeter and the hemoglobin concentration, 7.5 Gm. A transfusion was given, after which the remainder of the hospital course was uneventful. At the time of his discharge, on October 20, the van den Bergh test showed 1 mg. bilirubin per hundred cubic centimeters of serum. The hemoglobin concentration was 9 Gm., and the red blood cell count was 2,510,000 per cubic millimeter. The remainder of the data on the blood is in figure 2.

The patient has been followed at frequent intervals, and, when last seen on Dec. 27, 1948, seventeen months after operation, he was entirely asymptomatic. The only observation of interest was the persistent grade II systolic murmur heard best in the fourth left interspace. The murmur was believed to be rheumatic in origin. Results of blood studies are presented in figure 2.

COMMENT

The cases of these children present certain common features. The main similarities are that in both the illness began after "pneumonia"; both presented evidence of hemolytic anemia, with macrocytosis and a relatively high color index, though spherocytes were absent; both showed clinical jaundice, pronounced splenomegaly and hepatomegaly, and both had normal reactions on fragility tests. Finally, both showed a mild to serious decrease in the three formed elements of the blood, a relatively high reticulocyte count and hyperplastic bone marrow, with a predominance of erythroblasts. The obvious points of difference are as follows: B. S. was a girl, while T. R. was a boy; B. S. had probably been ill since infancy or early childhood, while T. R. had been sick for only five or six months prior to the present illness; B. S. had a family history of "blood disease" and T. R. did not; B. S. showed great decrease in size of the spleen with transfusions, while T. R. did not; the condition of B. S. showed practically no change in the course of the epinephrine tolerance test, but that of T. R. showed decided response. Finally, B. S. had only a temporary reaction to splenectomy, with a progressively downhill course for four or five months and death eight months after the operation, while T. R., when last seen seventeen months after splenectomy, was in excellent physical condition and had a normal blood picture.

It is felt that these 2 cases merit reporting because of the relatively few instances of the syndrome recorded in the literature, and because of the dramatic and life-saving response in certain cases to splenectomy. It is hoped that this report may stimulate interest in the syndrome of splenic panhematopenia.

No laboratory tests for specific hemolysins, agglutinins or a lysolecithin were done, as facilities were not available when these 2 patients were being studied. Splenectomy was offered to them as a last resort.

Doan and Wright [2] stated that the differential diagnoses which must be considered in the syndrome under discussion are threefold: (1) a hypoplastic bone marrow, either primary or secondary; (2) splenic panhematopenia, secondary to a constitutional pathologic process which involves the spleen, and (3) primary splenic panhematopenia on a congenital or familial basis. They stated that complete data from the epinephrine test and careful analyses of aspirated bone marrow should provide information on which to base an opinion and institute therapy. In the first two conditions splenectomy usually results in a temporary remission in the blood picture and clinical state; in the last-named condition, in which the spleen primarily is at fault, a prompt, complete and permanent reequilibration, both hematologic and clinical, may be anticipated.

Though the case of B. S. is presented as one of a primary panhematopenia, since no underlying cause for the syndrome was demonstrated, it is quite possible that the case should be classified under the second diagnostic group, as a condition secondary to some constitutional pathologic process. The results of splenectomy would bear this out.

The condition of T. R. falls into the third diagnostic group, as suggested by the results of splenectomy up to this time.

SUMMARY

Two cases of splenic panhematopenia are described. One of the patients has remained well for seventeen months after splenectomy. The difficulty of differentiating primary and secondary splenic panhematopenia is discussed. Splenectomy may be of value in selected cases.

Bowman Gray School of Medicine (7).

Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

FURTHER OBSERVATIONS OF AN INHIBITOR IN HUMAN SERUMS OF THE HYALURONIDASE PRODUCED BY A STRAIN OF HEMOLYTIC STREPTOCOCCUS. GEORGE J. FRIOU, J. Infect. Dis. **84**:240 (May-June) 1949.

Further studies were done on an inhibitor in human serums of the hyaluronidase derived from a strain of Streptococcus hemolyticus of group A, type 4. The titer of this inhibitor in the serum increased during convalescence in most of 50 cases of scarlet fever. The maximum titer of the inhibitor was reached more than fourteen days after the onset of the infection in most of the cases. The inhibitor was highly specific for the hyaluronidase of the group A streptococcus, and the changes in titer approximately paralleled the changes in titer of antistreptokinase and antistreptolysin O. An inhibitor with a similar specific effect on the hyaluronidase produced by group A streptococci was shown to be concentrated in pooled purified human gamma globulin. The inhibitor in whole serum was stable at 56 C. (132.8 F.) for relatively long periods. The distribution of titers among serums from infants and children was such as to suggest that transfer of the inhibitor from the maternal to the fetal circulation occurs, and that the passively acquired inhibitor is lost during the postnatal period. Certain of these findings differentiate this inhibitor from the inhibitor of testicular hyaluronidase currently under study in other laboratories. The findings reported here indicate that the inhibitor under study in this laboratory is probably of the nature of an antibody.

FROM THE AUTHOR'S SUMMARY.

CYSTEINE AND RELATED COMPOUNDS IN THE GROWTH OF THE YEASTLIKE PHASE OF HISTOPLASMA CAPSULATUM. S. B. SALVIN, J. Infect. Dis. **84**:275 (May-June) 1949.

No single amino acid was necessary for the growth of the mycelial and yeastlike phases of Histoplasma capsulatum. The mycelial phase also grew with ammonium as the sole source of nitrogen. A sulfide or sulfhydril group in a small organic molecule, preferably an amino acid, was essential for the growth of the yeastlike phase. Biotin was necessary for the development of the yeastlike cells, but with one exception had no effect on mycelial growth. The mycelial phase was changed to the yeastlike phase, and vice versa, at constant temperature (37 C. [98.6 F.]) by varying the contents of the culture medium.

FROM THE AUTHOR'S SUMMARY.

STUDIES ON THE SUPPRESSION OF FUNGUS GROWTH BY THIOUREA: III. THE EFFECTS OF PROTEIN FRACTIONS, AMINO ACIDS, AND THIOL COMPOUNDS. M. TAGER, H. B. HALE and T. S. DANOWSKI, J. Infect. Dis. **84**:284 (May-June) 1949.

The reversal of thiourea activity by human serum or plasma appears to be related to the nonalbumin fraction. Similar reversal was observed following the addition of substances which provide or reconstitute the sulfhydril groupings. The contrasting effects of the albumin and nonalbumin fractions of the serum or plasma proteins on thiourea activity are discussed.

FROM THE AUTHORS' SUMMARY.

INFECTIONS INDUCED IN MICE BY LOCAL APPLICATION OF STREPTOCOCCI AND PNEUMOCOCCI TO THE NASAL MUCOSA AND BY INTRAPULMONARY INSTILLATION. L. S. SONKIN, J. Infect. Dis. **84**:290 (May-June) 1949.

Streptococcus group C and Pneumococcus type I were deposited by means of a micrometer syringe device on the nasal mucosa, in the lung and in the esophagus of mice. Volumes were employed which permitted the original inoculum to be deposited and confined to the aforementioned sites without flowing into neighboring structures.

Beta-hemolytic streptococci, group C, were slightly more lethal to etherized mice when deposited on the nasal mucosa than when inoculated into the lungs. The median lethal doses of Pneumococcus type I by both routes in etherized mice were the same within the limits of error of the experiment but were higher than the median lethal doses of the streptococcus.

The variability in the data on the dosage mortality obtained with the pneumococcus indicates that titrations of mice with doses of this organism will not provide an accurate end point for quantitative comparisons of groups of data obtained by methods comparable to those described here. End points obtained with group C Streptococcus are satisfactory for this purpose.

Deposition of streptococcic cultures on the undamaged nasal mucosa caused a lethal infection in mice. Interesophageal inoculation failed to cause infection. All but 2 of 161 animals that died after intranasal inoculation with Streptococcus group C showed enlarged, purulent lymph nodes, whereas mesentric and inguinal nodes displayed little or no involvement. Only 2 mice of 52 autopsied after fatal intrapulmonary instillation and intravenous inoculation had similar pathologic involvement of cervical lymph nodes.

None of the mice that died after pneumococcic inoculations by any route had purulent cervical lymph nodes. Pneumococci were not observed on the nasal mucosa or in any of the tissues of the head and neck at any time between one hour after intranasal deposition and the onset of bacteremia ten to sixteen hours later.

The pulmonary infections in mice that died after intranasal inoculation was of an interstitial type, whereas in mice that died after intrapulmonary inoculation abundant bacterial growth occurred in the air spaces. The bearing of these findings on experimental air-borne infections is discussed.

FROM THE AUTHOR'S SUMMARY.

ISOLATION OF EASTERN EQUINE ENCEPHALOMYELITIS VIRUS FROM NATURALLY INFECTED MONKEY (MACACUS PHILIPPINENSIS). HARVEY R. LIVESAY, J. Infect. Dis. **84**:306 (May-June) 1949.

The clinical observations on the disease in the Philippine monkey are similar to those in known poliomyelitis, in that paralysis of the flaccid type is common in the hindlegs. In the more acute form of the disease the flaccid type of paralysis may be absent. The incubation period is usually shorter.

The eastern type of equine encephalomyelitis virus was isolated and identified as the causative agent of a natural disease in the native Philippine monkey (Macacus philippinensis).

FROM THE AUTHOR'S SUMMARY.

A STUDY OF THE MODE OF ACTION OF SUBSTANCES WHICH ENHANCE BACTERIAL INVASIVENESS. CURTIS SANDAGE and ORTON K. STARK, J. Infect. Dis. **84**:310 (May-June) 1949.

Preparations of gastric mucin and certain bacterial polysaccharides which have in common the capacity to enhance invasiveness of micro-organisms were shown

to increase capillary permeability in the guinea pig. Of the substances tested, only gastric mucin had a comparable effect in rabbits. The possibility that this capacity to increase capillary permeability is causally related to the action of pathogenizing agents is discussed. Objections are raised to the view that mucin enhances invasiveness by virtue of its coating effect on micro-organisms.

FROM THE AUTHORS' SUMMARY.

CULTIVATION OF THE LANSING STRAIN OF POLIOMYELITIS VIRUS IN CULTURES OF VARIOUS HUMAN EMBRYONIC TISSUES. J. F. ENDERS, T. H. WELLER and F. C. ROBBINS, Science **109**:85 (Jan. 28) 1949.

The authors found it possible to maintain the Lansing strain of poliomyelitis virus in human embryonic tissues (two and one-half to seven months' gestation) of three types: skeletal tissues from the extremities, intestine and brain. The virus seemed to retain its identifying characteristics and to multiply. It is postulated that the virus can be grown in tissues which do not contain intact neurons.

FORBES, St. Louis.

Metabolism; Infant Feeding; Milk and Other Foods

THE EFFECT OF SEVERE HEAT TREATMENT UPON THE AMINO ACIDS OF FRESH AND CURED PORK. J. F. BEUK, F. W. CHORNOCK and E. E. RICE, J. Biol. Chem. **175**:291 (Aug.) 1948.

Samples of fresh and cured pork were analyzed for their amino acid content before and after autoclaving at 112 C. (234 F.) for twenty-four hours. Assays were made for leucine, isoleucine, valine, methionine, tryptophane, cysteine, lysine, threonine, phenylalanine, arginine and histidine by microbiologic methods. This drastic treatment had no effect on any of the amino acids tested, except for cysteine, which was reduced to about one half of its usual value. It seems unlikely that the amount of heat applied to pork during normal cooking procedures could be any more destructive.

FORBES, St. Louis

METHODS FOR DETERMINING THE IRON CONTENT OF MILK. F. A. JOHNSTON, N. GELLMAN and J. STROM, J. Biol. Chem. **175**:343 (Aug.) 1948.

The authors' review their methods for determining the iron content of cow's milk and conclude that the results obtained, 0.33 to 0.39 mg. per kilogram, are valid.

FORBES, St. Louis.

LUGOL'S SOLUTION IN FAILING LACTATION. DAVID P. NICHOLSON, Brit. M. J. **1**:1029 (May 29) 1948.

Successful breast feeding depends greatly on the quantity and the differentiation of the tissues making up the breast. Dried thyroid gland has been used and there is evidence that it will increase breast milk flow as much as 20 to 30 per cent. This work was reported by Engel and also by Foeley. Robinson described her success in increasing lactation with the use of strong iodine (Lugol's) solution. Using approximately the same method as Robinson, the author obtained data on a series of 54 women to whom strong iodine solution was given, as well as on an adequate control series. After carefully following these patients, he came to the conclusion that strong iodine solution did not affect lactation and was unsuccessful in increasing the production of breast milk.

BIRDSONG, University, Va.

BLOOD PICTURE IN THE HYPOPROTEINEMIC STATES AS INFLUENCED BY AMINO ACID INFUSIONS. L. SALMI, Clin. pediat. **30**:101 (Feb.) 1948.

One hundred and fifty to 200 cc. of a 5 to 10 per cent solution of amino acids from hydrolyzed casein was given daily by rectum or intravenously to 10 children, who suffered from malnutrition, secondary anemia and low blood protein content. Six to ten days' treatment led to an increase in the red blood cell count, the hemoglobin content, the color index and the percentage of reticulocytes; the total blood protein content and the albumin to globulin ratio approached normal.

HIGGINS, Boston.

THROMBOPLASTIN IN HUMAN MILK. G. LENZI and M. ORLANDELLO, Clin. pediat. **30**:169 (March) 1948.

Human milk contains sufficient thromboplastin to cause definite shortening of the coagulation time of blood. The power of the milk to aid in clotting gradually diminishes on standing.

HIGGINS, Boston.

INTENSIVE TREATMENT WITH YEAST OF DEFECTIVE NUTRITION IN INFANTS. R. PACHIOLI, Clin. pediat. **30**:273 (May) 1948.

Ten "dystrophic" infants 1 to 7 months of age were given a dried yeast preparation in amounts of 17 to 42 Gm. daily, equivalent to 3 to 6 per cent of the daily food requirements, over a period of twenty-one to fifty days. Most of the infants gained weight and improved in color and general condition. The blood protein at first became lower under this regimen but later increased to normal amounts; in each child the albumin to globulin ratio increased. The percentage of sugar in the blood showed a small increase. The basal metabolic rate, initially low, became normal. The bone marrow smears showed a diminution of the erythroblastic elements as the anemia disappeared.

HIGGINS, Boston.

PRESERVATION OF RAW HUMAN MILK. FRIEDRICH, LINNEWEH, Med. Klin. **44**:166 (Feb. 11) 1949.

Streptomycin is placed in sterilized bottles so that when they are filled the drug is present in a concentration of 2 mg. per hundred cubic centimeters. In this manner exogenous Escherichia coli infection is avoided. Acidification and coagulation of the human milk are prohibited without the necessity for refrigeration. It has not been determined whether under such conditions other changes take place which reduce the biologic value, nor has the effect of streptomycin on the spore-bearing micro-organism been studied sufficiently, so that refrigeration cannot be regarded as superfluous as yet.

AMBERG, Rochester, Minn.

EFFECT OF DEFICIENT FOOD SUPPLY ON VITAMIN REQUIREMENTS OF VIENNA SCHOOL CHILDREN. C. SCHWARZ-WENDL, W. AUERSWALD and H. BORNSCHEIN, Wien. klin. Wchnschr. **25**:400 (June 25) 1948.

The deficiency of foods containing vitamin C corresponds with the vitamin C deficiency in the nourishment of Vienna school children. On account of the scarcity of potatoes in the diet, the ascorbic acid deficiency became manifest. Vitamin C deficiency was apparent in a control group who were receiving insufficient vegetables and fruit, in spite of the fact that they were receiving 15 to 30 mg. of ascorbic acid daily. It was also observed that when protein was extremely deficient in the diet it was necessary to double the vitamin C intake to provide an adequate amount.

In recent times the supply of bread in the diet has increased and seems to take care of the vitamin B requirements. Tests for vitamin A and D requirements were not feasible for technical reasons.

ABT and ABT, Chicago.

CHANGES OF THE SERUM POTASSIUM LEVEL IN THE COURSE OF DOUBLE GLUCOSE TOLERANCE TESTS. L. BARTA, L. BORSÓDI and Z. HORN, Paediat. danub. **4**:59 (Aug.) 1948.

It was observed that the potassium level of the serum increased sixty or ninety minutes after the administration of the first dose of dextrose. Following the second dose, that is, during the Staub-Traugott effect, potassium was in the blood but never at a level below the fasting value. This fact indicates that dextrose consumption during the Staub-Traugott effect takes place more rapidly and economically than after the first dose. This fact may confirm the observation that storage of carbohydrate in the liver is increased during the Staub-Traugott effect. The same conclusion was drawn by Horn and Barta and Sass-Kortsák from the changes in the difference between capillary and venous blood sugar levels.

Of course, in the evaluation of this data one has to consider that increased potassium mobilization is a defensive reaction aimed at maintaining the constant composition of the body fluids.

FROM THE AUTHORS' SUMMARY.

OBESITY IN CHILDREN: A CLINICAL-PROGNOSTICAL INVESTIGATION. HANS-OLOF MOSSBERG, Acta pædiat., 1948, vol. 35, supp. 2.

Weighty arguments speak for the common occurrence of a constitutional-heredofamilial factor in obese children, resulting in the difference in the degree of obesity and the point of time of onset in the instances of familial obesity, the variety of results on the study of heredity and, in certain cases, the characteristic size of the sella turcica on the roentgenogram.

The various investigations seem to show that the presence of a certain endocrine disturbance cannot be established as an etiologic factor in the obesity of children with the methods used.

Obese children show physical and mental development which, on the average, is clearly in advance of that of normal children of comparable ages, this being manifest by the bodily proportions and a number of bodily factors, such as weight at birth, stature, time of onset of the prepuberal acceleration of growth, development of puberty, age at menarche, basal metabolic rate, skeletal development and development of intelligence.

The results of the investigations on obese children with gigantism and dwarfism, respectively, should not be compared with the normal values for healthy children of comparable ages without taking into consideration the abnormal bodily proportions of the deformed children.

Children with Fröhlich-like obesity (adiposogenital-like dystrophy), irrespective of the distribution of fat and an eventual temporary hypogenitalism, do not exhibit any sign which with certainty distinguishes them from the large group of children with diffuse noncharacteristic obesity.

The prognosis in adulthood for untreated children is variable and dependent partly on the sex, partly on the degree of luxus consumption and partly on the degree of obesity at 7 to 13 years of age, with the poorest prospects for the more obese girls and the best prospects for the less obese boys.

FROM THE AUTHOR'S ABSTRACT.

Vitamins; Avitaminoses

THE EFFECT OF THE INGESTION OF HIGH LEVELS OF RIBOFLAVIN ON THE AMOUNT IN THE MILK AND URINE. P. B. PEARSON and B. S. SCHWEIGERT, J. Nutrition **34**:443 (Oct.) 1947.

Pearson and Schweigert observed that the oral administration of large amounts of riboflavin to goats and sheep increased the true riboflavin content of the milk by only about 26 per cent. By the fluorometric procedure the riboflavin values for the milk were approximately five times greater than the values obtained by the microbiologic method, and the fluorometric values for the urine were about twelve times higher. The riboflavin content of the milk as measured by microbiologic assay agreed well with the growth response of rats fed the milk as a source of riboflavin. When massive daily doses of 10 or 20 mg. of riboflavin were administered, the microbiologic and fluorometric values for the riboflavin content of the urine of rats were in good agreement. The same occurred in human beings fed 20 mg. of riboflavin per day. Evidently, goats and sheep fed large amounts of riboflavin form a fluorescent compound that is measured by the fluorometric procedure for riboflavin. The unidentified compound secreted into the milk and excreted by the renal pathway is not biologically active.

FREDEEN, Kansas City, Mo.

THE THIAMINE AND RIBOFLAVIN CONTENT OF WHOLE WHEAT, NONENRICHED AND ENRICHED FLOURS AND OF BREADS MADE THEREFROM. N. B. GUERRANT and O. B. FARDIG, J. Nutrition **34**:523 (Nov.) 1947.

Guerrant and Fardig conclude that flour enriched in accordance with the present formula is definitely superior to nonenriched flour with respect to thiamine and riboflavin content and is somewhat superior to whole wheat with respect to the level of these vitamins.

FREDEEN, Kansas City, Mo.

PRESERVATION OF CAROTENE IN DEHYDRATED VEGETABLES. A. W. HALVERSON and E. B. HART, J. Nutrition **34**:565 (Nov.) 1947.

Halverson and Hart found that a water content of 10 to 12 per cent and sealing will not only preserve the carotene well but also give a product resembling the original unsealed material in color, taste and aroma. It is suggested that probably the moisture levels required for maximum preservation of carotene will vary with the different vegetables and the method of dehydration employed.

FREDEEN, Kansas City, Mo.

THE EFFECT OF ADDED THIAMINE ON GROWTH, VISION, AND LEARNING, USING IDENTICAL TWINS. E. CHANT ROBERTSON, C. M. TATHAM, NORMA FORD WALKER and M. REID WEAVER, J. Nutrition **34**:691 (Dec.) 1947.

The authors administered 2 mg. of thiamine daily for four and a half months to half of 36 sets of identical twins, which resulted in an improvement in gains in weight and height and in manual dexterity and prolonged memory test scores that was of questionable statistical significance. The tests used for measuring vision, intelligence, reasoning, arithmetic ability, rote memory and code substitution gave results of no statistical significance. Twenty-five sets of twins were kept in the study for four and a half months longer. When they were again tested at the end of this period, no gains of statistical significance were evident in the results of any of the tests.

FREDEEN, Kansas City, Mo.

A Clinical Study of Avitaminosis A. Debarbrata Pal, Indian J. Pediat. **16**:1 (Jan.) 1949.

Vitamin A deficiency is the commonest avitaminosis in India. Seventy cases are presented, with tables showing the predominant manifestations in each. No follow-up study or laboratory work could be done.

McGuigan, Evanston, Ill.

Cutaneous Changes in the Rat Following Large Peroral Doses of Vitamin A. A. Studer and J. R. Frey, Schweiz. med. Wchnschr. **79**:382 (April 30) 1949.

Oral administration of large amounts of vitamin A to white rats produced generalized changes of the epidermis. The changes began after three to four doses, increased to about the thirteenth day and regressed slowly in spite of further administration. The histologic changes of the skin are discussed with the aid of good illustrations.

Amberg, Rochester, Minn.

Hygiene; Growth and Nutrition; Public Health

The Clinical Supervision of Child Development. Arnold Gesell, Wisconsin M. J. **48**:119 (Feb.) 1949.

"Development is the supreme function of the growing organism because it sums up all the life processes. Health, in infancy and childhood, must be defined as the condition which permits and promotes optimal development." In our complicated society development does not take care of itself but must be safeguarded.

Development manifests itself in three ways, anatomic, physiologic and behavioral. Behavior includes motor, adaptive, language and personal-social aspects. Supervision of development, including the making of a "behavior inventory," should become a routine feature of pediatric practice either by the pediatrician or by the general practitioner.

In differential diagnosis defective development, primary, secondary to destructive lesions or mixed, must be separated from deviated development due to such things as prematurity, endocrine dysfunction, selective sensory or motor handicaps, abnormal experience, deprivation or stress and personality defects.

"Developmental diagnosis may be defined, in summary, as a pediatric form of neuropsychiatry which utilizes clinical norms and functional tests of behavior to define the maturity, the integrity, and the personality traits of a growing action system. Developmental guidance applies the methods of developmental diagnosis to interpret the status and the individual needs of the growth process in infant and child." This seems a fundamental approach to a comprehensive program for the conservation of mental health.

Baird, Wauwatosa, Wis.

Children's Health Centres and Their Uses. Donald Paterson, Canad. M. A. J. **62**:39 (Jan.) 1950.

A children's health center should be associated with a large hospital or medical school. For good results, the services of all the usual consultative divisions are required. Such a setup makes the connection with a hospital or school mandatory. The health center should, however, be more than a hospital outpatient department; it should embrace community and public health services.

McGuigan, Evanston, Ill.

NEW METHOD FOR EVALUATION OF BODY WEIGHT, WITH CONSIDERATION OF THE CONSTITUTION BY UTILIZATION OF THE CHEST CIRCUMFERENCE. H. TRÄBERT, Med. Klin. **44**:431 (April 8) 1949.

The author introduces an individual weight correlator similar to a slide rule on the basis of a formula in which normal weight equals body length multiplied by circumference of chest divided by an age constant, or rather the reciprocal of this age constant. Or simplified, the age in years is subtracted from 45 and the result multiplied by 8, so that

$$P=0.125\left(\frac{45-A}{L\times B}\right)$$

in which P is the normal weight in kilograms, L is the length in centimeters, B is the circumference of the chest in centimeters and A is the age in years. Subnormal weights from about 5 per cent on are of clinical significance. The correlator permits direct reading of the deviation of the individual weight from the normal in percentage. The age scale starts with 1 year.

AMBERG, Rochester, Minn.

Prematurity and Congenital Deformities

LOUISIANA'S PROGRAM FOR THE CARE OF THE PREMATURE INFANT. SIDNEY S. CHIPMAN and WALDO L. TREUTING, Pediatrics **5**:45 (Jan.) 1950.

Statistics for Louisana show that a large number of infants are born prematurely and that the death rate among these infants is high. The Louisiana program for the care of the premature centers around Charity Hospital in New Orleans and is the result of combined cooperative effort of the hospital, the state and city health departments, the Children's Bureau and the two medical schools in the city.

The large unit for premature infants at the hospital has been rebuilt and divided into four large air-conditioned nurseries in which ample floor space is available for each infant. One nursery is used for the care of the larger, more mature infants and another, functionally separated from the others, is devoted to the care of those infants with a communicable disease. All other premature infants are admitted to one of the two remaining nurseries.

It is recognized that a comprehensive program for the care of prematurely born infants must include case finding, hospital placement, training of personnel, home investigation and follow-up study. To date, in this state, special emphasis has been placed on the organization of a training center in order that skilled personnel will be available to aid in the development of the other phases of the program in all areas of the state.

FROM THE AUTHORS' SUMMARY.

CRANIO-FACIAL DYSOSTOSIS OF CROUZON: REPORT OF A CASE IN WHICH THE MALFORMATION OCCURRED IN FOUR GENERATIONS. JAMES H. FLIPPEN, Pediatrics **5**:90 (Jan.) 1950.

A case of craniofacial dysostosis of Crouzon hypertelorism occurring in a 4 year old girl is described. The pedigree of this patient is of particular interest because the deformity is known to have been present in 10 members of four generations, thus demonstrating its hereditary nature. Because 10 of the progeny were afflicted, the pedigree is interpreted as meaning that the disorder is the expression of a heterozygous, dominant trait. The patient was considerably benefited by the operation advocated by Faber and Towne for premature cranial synostosis, as modified by Ingraham.

FROM THE AUTHOR'S SUMMARY.

GROWTH PATTERN OF PREMATURELY BORN INFANTS. KURT GLASER, ARTHUR H. PARMELEE and E. B. PLATTNER, Pediatrics **5**:130 (Jan.) 1950.

One hundred and sixty-three prematurely born infants were observed during the first eight months of their lives and their growth patterns were studied. The maximal daily gain in weight and length occurred during the second to sixth months of life. The peak of the daily gain in weight occurred somewhat later in the smaller infants. The growth in length ran a similar but less pronounced course. The boys exceeded the girls in weight and length at 8 months of age. Negro and white children grew at a similar rate, with the Negroes slightly lower in weight beginning with the fourth to sixth months. Growth in circumference of the head and sitting height was found to be parallel, with a slight deceleration in head growth during the second part of the observation period. The possible influence of the dietary management of the children is discussed, and the observations are presented in tabular and graphic forms.

FROM THE AUTHORS' SUMMARY.

A RARE CONGENITAL MALFORMATION. D. P. R. KEIZER and H. J. JENS, Maandschr. v. kindergeneesk. **17**:301, 1950.

A boy, 2 months old, was born with the left arm showing seven fingers, a double carpus and two ulnas. The description is illustrated by two roentgenograms.

FROM THE AUTHORS' SUMMARY.

Newborn

THE INITIATION OF A ROOMING-IN PROJECT AT THE GRACE-NEW HAVEN COMMUNITY HOSPITAL. EDITH B. JACKSON, in Senn, M. J. E.: Problems of Early Infancy, Transactions of the First Conference, March 3-4, 1947, New York.

Rooming-in was tried as a means of avoiding parental difficulties with newborn children in the home and later problems arising from failure of parents to understand infant behavior at the time they took the newborn babies home from the hospital. A unit of four beds has been used in this way since October 1946, with unanimous appreciation on the part of the mothers. At the time of publication it was too early for evaluation of the success of this plan.

McGUIGAN, Evanston, Ill.

ROOMING-IN AS A FAMILY EXPERIENCE AT THE GRACE-NEW HAVEN COMMUNITY HOSPITAL. RICHARD W. OLMSTED, in Senn, M. J. E.: Problems of Early Infancy, Transactions of the First Conference, March 3-4, 1947, New York.

The fundamental objective of the rooming-in project is the fostering of more well informed, well adjusted, happy families. After four months, Olmsted states his belief that this objective is being reached by bringing the family together in a common understanding of the newborn child and his needs. The pediatrician can also observe the family's reaction and thus form a better basis for professional guidance.

McGUIGAN, Evanston, Ill.

PATHOGENIC INFLUENCES OF MATERNAL ATTITUDES IN THE NEONATAL CHILD. EMMY SYLVESTER, in Senn, M. J. E.: Problems of Early Infancy, Transactions of the First Conference, March 3-4, 1947, New York.

Understanding and modification of maternal attitudes require an approach which recognizes that both mother and child have to be regarded as a single dynamic unit, and that maternal attitudes are shaped within the historical process of the mother's entire life, with particular stress on her own infantile experiences.

McGUIGAN, Evanston, Ill.

THE IMPORTANCE OF MOTHER AND BABY ROOMING TOGETHER (FOR THE MOTHER, FATHER, FAMILY, AND DOCTOR). MARGARET E. FRIES, in Senn, M. J. E.: Problems of Early Infancy, Transactions of the First Conference, March 3-4, 1944, New York.

Advantages of the rooming-in plan for the mother, baby, physician, father and family are listed.

McGUIGAN, Evanston, Ill.

THE ROOMING-IN PROJECT: AN EDUCATIONAL OPPORTUNITY FOR THE STUDENT IN NURSING. KATE HYDER, in Senn, M. J. S.: Problems of Early Infancy, Transactions of the First Conference, March 3-4, 1947, New York.

The practical experience gained in two weeks in the rooming-in service is of great value to the student nurse. Interest is primarily stimulated by the naturalness and normalcy of the situation in the rooming-in unit on the part of all concerned.

McGUIGAN, Evanston, Ill.

INTESTINAL OBSTRUCTION IN THE NEWBORN. M. A. KHARADLY, J. Roy. Egyptian M. A. **30**:289 (June) 1947.

Kharadly presents a case of intestinal obstruction in a newborn infant caused by a membrane occluding the lumen of the duodenum in its lower part. He discusses briefly the developmental causes of congenital obstructions of the bowel and their treatment and prognosis.

McGUIGAN, Evanston, Ill.

FETAL AND NEONATAL ERYTHROBLASTOSIS AND THE RH FACTOR. G. DE TONI, Policlinico inf. **15**:289 (July) 1947.

In spite of its fundamental inaccuracy, the term erythroblastosis has been accepted to include four pathogenically related syndromes of great current interest: fetal hydrops, icterus gravis neonatorum, anemia of the newborn and, most recently, hepatic cirrhosis in macerated fetuses. The history of their recognition is briefly reviewed. Only after the discovery of the Rh factor and of its participation in the antigen-antibody mechanism common to all these syndromes was it possible to bring them together into a single etiopathogenic concept. Important discoveries have resulted from the investigations stimulated by Levine, Landsteiner and Wiener. At the same time, many fundamental questions remain unanswered; they are examined by the author in the light of recent evidence. Treatment and prophylaxis are discussed.

FROM THE AUTHOR'S SUMMARY.

FEVER IN NEWBORN INFANTS. MAURICE LUST, Acta pædiat. belg. **1**:122, 1946-1947.

Temperature elevations in newborn infants can be attributed to various causes.

1. Temperature regulation in newborn infants is not sufficiently perfect, so that overheating may occur easily. The humidity and temperature of the room or bassinet must be considered. Although the author cites reports from the literature concerning death due to overheating, he himself has never seen such a case.

2. Infections tend to cause fever (cutaneous infections ordinarily excepted). In debilitated children one may observe subnormal or normal temperatures which may actually correspond to fever in healthy children.

3. Intracranial hemorrhage with meningocerebral irritation is another cause. Irritation of the heat regulation center can cause fever which may be either benign, if it is accompanied with peripheral vasodilatation and perspiration, or

serious, if these reactions do not occur. Subdural hemorrhages are most frequent. In syphilitic and premature children, intracerebral or intraventricular hemorrhages occur oftener. Symptoms of intracranial hemorrhage are apathy, anorexia, cephalic cry, vomiting, convulsions, tense or normal fontanel, hyperthermia, nystagmus and hyperirritability of the muscles. Spinal puncture is diagnostic, but blood drawn accidentally may confuse the picture and some hemorrhages do not reach the site of puncture. The fluid is characteristically of large amount and red or reddish with yellow supernatant fluid on centrifugation. Treatment consists of frequent small lumbar punctures.

4. Nutritional disturbances constitute the last possibility discussed. This type of fever was listed under different etiologic headings by various authors. Lust saw it only in breast-fed children, never in those fed with cow's milk or the breast milk of wetnurses. He claims that it responds rapidly to oral water intake but states that there are no signs of dehydration other than the physiologic loss of weight. The high protein and mineral content of the colostrum of the mother in the presence of dehydration is another factor to be considered. A water supplement during the first days of life will prevent the fever. GLASER, Chicago.

Acute Contagious Diseases

THE COMPLICATIONS OF MUMPS. DESMOND LAURENCE and DONALD MCGAVIN, Brit. M. J. **1**:94 (Jan. 17) 1948.

An epidemic of mumps (235 cases) was investigated with the view of determining the incidence of complications and any permanent after-effects resulting from them. Eight cases of meningoencephalitis are described. It was found that recovery tended to be slow and that when paralysis of the facial nerve occurred recovery was incomplete.

The incidence of orchitis was 26 per cent. There were no cases of complete testicular atrophy following this complication, but 42 per cent showed minor degrees of atrophy. Sexual activity was unimpaired. Pancreatitis of slight degree occurred in 8 per cent of the cases. BIRDSONG, University, Va.

METHODS OF EVALUATION OF THE MOTOR DEFICIT IN PATIENTS WITH POLIOMYELITIS. M. LIBERO, Clin. pediat. **30**:28 (Jan.) 1948.

The methods outlined are similar to and largely based on those in use in North America. HIGGINS, Boston.

PARALYSIS OF THE FACIAL NERVE DUE TO POLIOMYELITIS. D. CIRILLO, Clin. pediat. **30**:108 (Feb.) 1948.

Of 783 children with acute poliomyelitis seen at the pediatric clinic at Padua, Italy, over a period of seventeen years, 112 or 14.3 per cent showed paralysis of the facial nerve; 101 of these had bulbar poliomyelitis. Of the cranial nerves, the third was involved in 3 cases, the sixth in 15, the seventh in 81 and the twelfth in 2. Boys were more frequently affected than girls. Older children were more prone to show paralysis of the facial nerve than the younger ones. It occurred more frequently in some epidemics than in others. HIGGINS, Boston.

LEUKEMOID REACTION IN WHOOPING COUGH. G. LENZI, Clin. pediat. **30**:232 (April) 1948.

The finding of a high white blood cell count, with immature granulocytes and red blood cells, as well as lymphocytosis, asthenia and an enlarged liver, is an

indication of intoxication and parenchymal injury in patients with whooping cough. These abnormalities in the blood disappear synchronously with the other symptoms as the patient's condition improves.

HIGGINS, Boston.

POLIOMYELITIS IN THE PROVINCE OF UDINE IN THE FIVE YEAR PERIOD, 1942-1946. S. STEFANINI and G. MINCIOTTI, Clin. pediat. **30**:259 (April) 1948.

Of 263 cases of poliomyelitis in the province of Udine, Italy, in the years 1942 to 1946, 154 were of boys and 129 of girls. All but 23 of the patients were under 5 years of age. One hundred and ninety-six cases occurred in the months of June, July, August, September and October, and 80 per cent of the patients had some paralysis of the lower limbs. The largest number of cases was in the year 1946. The disease was predominant in the plains of the province rather than in the hilly and mountainous terrain. In the plains there was much water in the summer months, though for the most part it was not potable; simultaneously, there were epizootics involving the cattle, chickens and ducks.

HIGGINS, Boston.

TONSILLECTOMY IN DIPHTHERIA CARRIERS. K. GRAF, Schweiz. med. Wchnschr. **78**:75 (Jan. 31) 1948.

The conservative treatment of the diphtheria carrier has not been followed by the desired results. The author is of the opinion that persistence of diphtheria bacilli depends on the presence of the disease in the mouth and nasal cavities, and that tonsillectomy and removal of the adenoids, when properly performed, nearly always eliminates the organisms. He also maintains that in cases in which the patient has been ill with diphtheria and the bacilli have not disappeared by the eighth week following recovery from the disease the operation may be performed. He recognizes that before operation conservative methods may be tried to eliminate the bacilli. He mentions various antiseptics, especially penicillin. He recommends that penicillin be used through injection or as a nasal inhalation or spray. If these methods do not succeed after three to four weeks' trial, operation should be resorted to. He is of the view that while the organisms may persist for a number of days after the operation, in most cases fourteen days after removal of the tonsils and adenoids bacilli are no longer found by cultural methods.

ABT and ABT, Chicago.

TREATMENT OF POLIOMYELITIS. H. ZELLWEGER, Schweiz. Med. Wchnschr. **78**:176 (Feb. 28) 1948.

The advances in the treatment of poliomyelitis are to be found mostly in the field of physical therapeutic methods. This is true especially in the patients in whom the movements of the lungs are affected and in whom artificial respiration becomes necessary. In the severest forms of paralysis of respiratory muscles atelectasis almost always occurs and in a short time leads to respiratory insufficiency and death. In these patients the so-called iron lung serves to ventilate the lungs. Obviously, in paralyses of the respiratory and circulating centers the iron lung can be of no help. The use of this respirator must be carefully controlled and artificial respiration must not be given continuously. One should attempt to bring the patient to respiratory effort without the assistance of the respirator.

The old method of treating the acute attack of poliomyelitis by immobilizing extremities caused a loss of muscular function. In paralyzed muscles there are circulatory disturbances, venous stasis and, as a result, nutritional disturbances of the damaged areas leading eventually to degenerative changes in the muscle substance. By methods of immobilization an atrophy of muscular tissues occurs, involving even muscle fibers which were not affected by poliomyelitis virus. These

atrophic processes are preventable by the modern active physical therapy. The author is of the opinion that in the acute inflammatory phases application of hot packs is of value.

As soon as the meningeal irritation and the pain have disappeared, physical therapy should be intensified. Often, perhaps always, there are in the paralyzed muscles large and small areas of intact muscle fibers that can be reactivated and caused to function. The author also recommends active motion in a water-filled bath or pool. The improvement of the patient causes a better mental attitude, an important factor in the treatment of these conditions. The author also calls attention to the fact that delayed growth in the extremities may result from the involvement of trophic centers in the spinal cord; an arm or a leg may be shortened. He concludes by stating that poliomyelitis therapy is in many respects more satisfactory than in previous years. It is true, he writes, that we cannot cure all paralyses but it is to be hoped that many patients not too severely paralyzed may be so improved that they become active and useful members of society.

ABT and ABT, Chicago.

HISTOPATHOLOGIC OBSERVATIONS ON APPENDICITIS IN MEASLES. R. FONTAINE, P. MANDEL and G. APPRILL, Wien. klin. Wchnschr. **28**:445 (July 16) 1948.

The authors record data on 50 patients who showed the classic symptoms of appendicitis during an attack of measles. The diagnosis was easily made. These patients showed nervousness; the reflexes were lively. Of these 50 patients, 30 displayed general nervous disturbances, whereas 20 had only local signs. Of the 30 with nervous symptoms, 11 made complete recovery after operation without residual nervous symptoms, though 18 showed more or less improvement after the operation. In the microscopic examination of the removed appendix no ulceration or phlegmonous inflammation was observed. The lymphatic tissue was increased. There was also an increase in the number of epithelial giant cells that tended to undergo degeneration. In short, the observations consisted of (1) giant cells in the lymph follicles and in the region of the mucous membrane and (2) an increase of nuclei in the epithelial cells, with degenerative changes in the nuclei.

ABT and ABT, Chicago.

Acute Infectious Diseases

CONGENITAL MALARIA IN TWO INFANTS. K. C. CHAUDHURI, Indian J. Pediat. **14**:117 (July) 1947.

A report of 2 cases of malaria in infants, one 6 weeks and one 4 weeks of age, is presented. Both had been ill since shortly after birth, and both mothers had serious attacks of malaria before and during pregnancy. Both recovered quickly on treatment with quinine. It is recommended that quinine be given in small doses at frequent intervals and that a week's course with this drug be followed by three to five days' treatment with pomaquine naphthoate U. S. P. (plasmochin®).

MCGUIGAN, Evanston, Ill.

SCHISTOSOMIASIS: AN EDUCATIONAL PROBLEM. J. A. KIESER, South African M. J. **21**:854 (Nov. 22) 1947.

Kieser points out that schistosomiasis may seriously interfere with a child's mental processes and lead to educational difficulties. These mental symptoms may be so pronounced as to cause a child to be considered mentally defective. The picture clears promptly on treatment. Six cases are cited.

MCGUIGAN, Evanston, Ill.

COADJUVANT TREATMENT OF TETANUS WITH PURIFIED CHONDODENDRON TORMENTOSUM EXTRACT (INTOCOSTRIN®). GUSTAVO SIMON AND MARIA ELSA IGLESIAS, Arch. de Pe. D. Uruguay **11**:592 (Nov.) 1947.

The authors report favorable results in a case of generalized tetanus which was treated with purified Chondodendron tormentosum extract (intocostrin®), in addition to antitetanic serum and penicillin. To a child 6 years of age, weighing 20 Kg., they administered 15 mg. of the drug three times a day for nine days. No alterations were seen in the vertebrae in roentgenograms taken before and after the treatment. In the authors' opinion this drug is useful for attenuating or eliminating the spasms of tetanus and their sequelae.

KALISKI, San Antonio, Texas.

INTESTINAL PERFORATION IN TYPHOID IN CHILDREN. OLIVER BALSAS U., Rev. chilena de pediat. **4**:245 (April) 1947.

Fourteen cases of intestinal perforation during typhoid in children are reported, with a mortality rate of 66 per cent. All the children were operated on. The author observed this complication most frequently in the third week of the disease, irrespective of whether the child's condition was clinically severe or mild. The symptoms and differential diagnosis are discussed. The author calls attention to the severity of this complication and expresses his opinion that the best results were obtained when diagnosis was made early and when surgical treatment was employed early.

KALISKI, San Antonio, Texas.

TETANUS FOLLOWING APPLICATION OF A PLASTER BANDAGE. OLGA BERKOVÁ, Pediat. listy **2**:259, 1947.

In a girl 11 years of age who was treated with a plaster bandage for fungus of the talocrural joint, tetanus developed which manifested itself first in the affected limb. The child recovered.

FROM THE AUTHOR'S SUMMARY.

Chronic Infectious Diseases

THE TREATMENT OF MILIARY TUBERCULOSIS WITH PROMIZOLE. EDITH M. LINCOLN, SAMUEL STONE and OLGA R. HOFFMAN, Bull Johns Hopkins Hosp. **82**:56 (Jan.) 1948.

Promizole® (4, 2'-diaminophenyl-5'-thiazolesulfone) was used for 5 consecutive patients with tuberculous meningitis without beneficial effects. Of 5 consecutive patients with acute generalized miliary tuberculosis treated with promizole,® 2 died forty-three days and four and a half months after the beginning of treatment. Three children showed complete recession of roentgenologic evidence of miliary tuberculosis and were alive thirty and thirty-three months after the beginning of treatment. They are still being given maintenance doses of promizole.® Promizole® has goiterogenic properties and an accelerating effect on secondary sex characteristics. No toxic effects were observed which required permanent discontinuance of treatment with the drug. Three protocols are given. The article is well illustrated and should be read by those interested in this problem.

LYTTLE, Los Angeles.

BCG Vaccination in All Age Groups: Methods and Results of a Strictly Controlled Study. Sol Roy Rosenthal, Eleanor I. Leslie and Erhard Loewinsohn, J. A. M. A. **136**:73 (Jan. 10) 1948.

BCG is safe and results of several studies are presented to show that it is effective in preventing tuberculosis. Practically all complications are avoided by use of the multiple puncture method. In the opinion of the authors, persons of susceptible races (Negro and Indian) and those unduly exposed to tuberculosis in all age groups would be benefited by vaccination.

Kimball, Evanston, Ill.

Congenital Toxoplasmosis. B. H. Kean and Robert G. Grocott, J. A. M. A. **136**:104 (Jan. 10) 1948.

The case history and autopsy observations, including photomicrographs of sections from the various organs, of a 9 hour old premature infant, weighing 1,070 Gm., are presented. Parasites were observed in the brain, spinal cord, eye, fifth cranial nerve, femoral nerve, kidney, nerves of the urinary bladder and skeletal muscles of the tongue, cheek, chest, leg and back. Latent infection could not be demonstrated in the mother, father or a 20 month old well sibling. On tenuous grounds the possibility is suggested that pigeons may act as an animal reservoir.

Kimball, Evanston, Ill.

Penicillin Therapy of Late Congenital Syphilis. Ralph V. Platou and John T. Kometani, Pediatrics **1**:601 (May) 1948.

Though no valid comparisons can be made until more patients have been treated and followed for a longer time, it seems to us that penicillin used alone is at least as effective as any other single agent for the treatment of late congenital syphilis. The extent to which treatment or time alone contributes to improvements cannot yet be stated. Most of the clinical and serologic indications of healing developed slowly; in only a few patients with the most superficial lesions were there objective signs of improvement during therapy.

The treatment schedules we employed are similar to those previously recommended for infants. At present, we advise a total dosage comprising at least 100,000 units of commercial penicillin per kilogram of body weight, divided into 100 equal intramuscular injections and given at two to three hour intervals around the clock for eight or more days. Therapeutic reactions, entirely febrile in nature, have all been transient and benign. There were no deaths. We believe that the simplicity, safety and convenience of these plans make them preferable to the more costly, hazardous and time-consuming older methods; furthermore, they effectively curtail the appallingly high delinquency rates formerly prevailing.

Results were significantly better for children treated under 6 years of age than they were for older children, and they were also better for those who had normal spinal fluid before treatment. Results were suggestively, but not significantly, better among those for whom the larger dosage schedules were used. Outcome was significantly worse in those who had received previous treatment of any sort. There were just 3 relapses—2 defined only serologically and 1 indicated by a questionable recurrence of interstitial keratitis.

About a quarter of the reactions of those with latent congenital syphilis became seronegative. The poorest results ensued for patients with clinical neurosyphilis; 2 children from this group continued to exhibit definite deterioration. For interstitial keratitis, results were most gratifying in 2 patients treated within a month of onset. Seventy-two per cent of all patients with late congenital

syphilis so far treated with pencillin and followed for more than two months are clinically well and have negative serologic reactions or progressively declining titers.

FROM THE AUTHORS' SUMMARY.

MULTIPLE CYSTIC TUBERCULOSIS OF THE BONES. McLEMORE BIRDSONG and CAMILLUS S. L'ENGLE JR., Pediatrics 1:767 (June) 1948.

Multiple cystic tuberculous lesions of bone are considered uncommon, this case being the fourteenth to be reported in the pediatric literature.

The case was of a 13 month old child who was admitted to the University of Virginia Hospital, Charlottesville, Va., with complaint of subcutaneous swellings and fever of eight months' duration. The first swellings were noticed at 5 months of age in the axilla and groin on the right leg and side of the head and in the fingers. They never separated or drained. He had been seen elsewhere, and a biopsy specimen from a gland in the neck was reported as tuberculous.

Physical examination revealed an ill child with the aforementioned lesions. The liver and spleen were moderately enlarged. The routine laboratory work was not revealing and tuberculin skin tests, with both human and bovine material, gave negative reactions. Biopsy material from the bone revealed the typical picture of tuberculosis, and the tuberculous bacilli were recovered. Roentgenologic study showed many cystic areas in bones throughout the body.

FROM THE AUTHORS' SUMMARY.

TUBERCULOUS MENINGITIS AND STREPTOMYCIN. C. B. RICH and A. J. SAMUELS, Canad. M. A. J. 58:282 (March) 1948.

A case of a child with tuberculous meningitis treated with streptomycin is presented in detail. Treatment was continued over a period of four months, both intramuscularly and intrathecally. Following this administration of the drug was continued intramuscularly until treatment had lasted nine months. The child appeared to recover from his infection, but at 3 years of age he showed pronounced mental retardation and was unable to sit up.

McGUIGAN, Evanston, Ill.

BCG VACCINE IN THE PREVENTION OF TUBERCULOSIS. B. McKONE, Canad. M. A. J. 58:575 (June) 1948.

A brief summary of the development and use of BCG vaccine is presented. The vaccine is stated to be harmless and of definite value in the prevention of tuberculosis. Its use is recommended for persons who must live or work in a tuberculous environment: sanatorium workers, children whose parents or other close relatives contract the disease and girls in nursing schools.

McGUIGAN, Evanston, Ill.

A CASE OF PULMONARY AND MENINGEAL TUBERCULOSIS. G. W. WOOD and J. A. SCOTT, Canad. M. A. J. 59:67 (July) 1948.

A case of pulmonary tuberculosis with meningeal involvement in an infant is reported. Treatment with streptomycin was begun with the child moribund, and was continued for a total of five and a half months. The child at the end of this period of therapy appeared clinically well, though the pulmonary lesion had not cleared.

McGUIGAN, Evanston, Ill.

A Case of Tuberculous Meningitis Treated with Streptomycin and Promin. R. R. MacGregor, Canad. M. A. J. **59**:69 (July) 1948.

A 7 year old boy with tuberculous meningitis was treated for five months with streptomycin and promin® (sodium p, p'-diaminodiphenylsulfone-N, N'didextrose sulfonate), at which time he appeared well. After six months, administration of streptomycin was discontinued. Seven months after the appearance of symptoms, the boy appeared perfectly well.

McGuigan, Evanston, Ill.

Diseases of Blood, Heart and Blood Vessels and Spleen

Combined Use of Angiocardiography and Cardiac Catheterization in the Diagnosis of Congenital Anomalies of the Cardiovascular System. Arnold L. Johnson and Donald L. McRae, Pediatrics **2**:643 (Dec.) 1948.

Cardiac catheterization and angiocardiography are two established methods of investigation in congenital anomalies of the heart and great vessels. Each has a useful place in elucidating the anatomic and physiologic complexities of cardiac malformations. Where both are required, we followed the cardiac catheterization with an angiocardiogram. After the catheter was withdrawn, a cannula was tied into the vein in readiness for the injection of dye. The hazard of either procedure did not appear to be increased thereby.

Cases of cyanotic children with congenital cardiac anomalies are presented to illustrate the use of the two methods in demonstrating the nature of the outflow tract of the right ventricle and the pulmonary artery. It has been possible to demonstrate pulmonary stenosis in association with poststenotic dilatation. A further case is presented of a mass in the middle mediastinum. The right portion of the mass was filled with dye from the superior vena cava, and from data obtained on catheterization it was apparent that arterialized blood was entering the mass. It was, therefore, suggested that one or more pulmonary veins drained into the superior vena cava, and that the right portion of the mass was an aneurysm of the superior vena cava or of a pulmonary vein. The case illustrates the way in which the two procedures may contribute special data in a difficult diagnostic problem of an acyanotic child with cardiovascular malformation.

From the Authors' Summary.

An Epidemic of Infectious Lymphocytosis with Diarrhea. M. G. Peterman, J. D. Kaster, Eli A. Gecht and G. L. Lembert, Pediatrics **3**:214 (Feb.) 1949.

An epidemic of 28 cases of infectious lymphocytosis limited to the wards of a children's home and the pediatric service of a general hospital is reported. A review of the literature is included. The disease was characterized by an elevation in the leukocyte count, with an increase in the number of small mature lymphocytes and an absence of prominent symptoms and signs. The first case was discovered by a routine blood cell count. Two cases are reported in detail. Sixteen of the children had mild intermittent diarrhea. The white blood cell count ranged from 18,900 to 147,000 per cubic millimeter and lymphocytes from 64 to 94 per cent. Leukemia, infectious mononucleosis, whooping cough and diseases causing a high leukocyte and lymphocyte count were excluded by clinical and laboratory evidence.

From the Authors' Summary.

CYANOSIS IN INFANTS WITH NITRATES IN DRINKING WATER AS CAUSE. WILL E. DONAHOE, Pediatrics **3**:308 (March) 1949.

Seven cases are reported in which idiopathic cyanosis or cyanosis of undetermined origin cleared with the discontinuance of the use of well water suspected to contain an excess of nitrates. Two of these babies showed slight recurrence within a week. In 1, the cyanosis cleared when use of milk from cows' drinking the water was stopped, and in the other, a nursing baby, the cyanosis disappeared when the mother discontinued use of the contaminated water and milk. From these cases it is presumed that cyanosis may develop in infants drinking water or milk from cows or from nursing mothers drinking milk or water containing an excessive amount of nitrates. Cyanosis due to methemoglobinemia will clear with the discontinuance of the use of waters heavily laden with nitrate. Oxygen was administered but had no effect. In severe cyanosis intravenous administration of methylene blue in the dosage of 1 to 2 mg. per kilogram of body weight is recommended.

FROM THE AUTHOR'S SUMMARY.

PEDIATRIC ASPECTS OF HEMOPHILIA. ARMAND J. QUICK, Pediatrics **3**:312 (March) 1949.

The basic defect in hemophilia is inadequate production of thrombin due to congenital lack of thromboplastinogen, as reported in recent studies. By means of a new test which measures the prothrombin consumed in coagulation, the available thromboplastinogen in the plasma can be estimated. This test serves as one of the most specific means now available for the diagnosis of hemophilia. The coagulation time may occasionally be misleading. The clinical history and the record of heredity are important. The hemophilic child must be protected against injury. When bleeding occurs, pressure and cold should be applied immediately. If this fails, plasma or fresh whole blood transfusions are indicated. For an emergency operation, the patient first should receive plasma or blood and the effect should be determined by the prothrombin consumption test to determine the need for subsequent transfusions.

FROM THE AUTHOR'S SUMMARY.

ANTEPARTUM DIAGNOSIS OF CONGENITAL ANOMALY OF THE HEART: CASE REPORT WITH A REVIEW OF THE LITERATURE. BEDFORD H. BERREY and RICHARD G. HELMAN, Pediatrics **3**:504 (April) 1949.

A case report and a review of the literature are presented. A white woman, aged 39 years, who had had 12 children after 20 pregnancies, began regular attendance at the prenatal clinic at four months' gestation. The first trimester was uneventful, with no illness of any kind. The past history, with exception of scarlet fever and tonsillitis in childhood and suspected tuberculosis (never proved), was noncontributory. Her physical condition was good. The patient had had several miscarriages and induced abortions. Nine children were living and well.

Fetal heart tones were noted during the initial examination, and nothing abnormal was heard then or at any subsequent visit until one hour after her admission to the hospital during active labor. Then a noisy, blowing, machinery-like systolic murmur was noted over the entire left side of the abdomen, not synchronous with the uterine or placental souffle. The fetal heart rate was 180 per minute, with the maternal pulse rate 88 to 92. Various therapies were employed after birth with no appreciable results and the infant was given oxygen constantly until death, thirty-six hours after birth. After a normal birth, the baby had the same type murmur heard ante partum, with a diastolic component and a palpable systolic thrill. Multiple

external congenital anomalies were present. At autopsy, a congenitally anomalous heart, with intraventricular septal defect, quadricuspid aortic valve, a common pulmonary and aortic artery, patent ductus arteriosus and patent foramen ovale, was observed, confirming the antepartum suspicion of intraventricular septal defect and patent ductus arteriosus. In addition, multiple other anomalies of jaw, ear, right femur, palate, intestinal tract and genitourinary tract were noted.

FROM THE AUTHORS' SUMMARY.

OBSERVATIONS ON ONE HUNDRED AND SEVENTEEN PATIENTS OPERATED ON FOR CONGENITAL PULMONARY STENOSIS. J. FRANK DAMMANN JR., STANLEY GIBSON and WILLIS J. POTTS, Pediatrics **3**:575 (May) 1949.

One hundred and seventeen patients with congenital stenosis or atresia of the pulmonary artery were operated on at the Children's Memorial Hospital, Chicago. An aortic-pulmonary anastomosis was accomplished in 105 patients with 10 deaths, a mortality of 9.5 per cent. Exploratory operations were performed on 12 patients, with a mortality of 50 per cent. The over-all mortality was 13.8 per cent. The commonest cause of death was cerebral anoxia. Avoidable surgical complications accounted for 2 deaths. There were 108 patients with a tetralogy of Fallot, 6 patients with tricuspid atresia, 1 with Eisenmenger's syndrome, 1 with a transposition of the great vessels and 1 with a pure stenosis of the pulmonary valve. In atypical patients the murmur may be absent or different in quality or location. The former means pulmonary atresia; the latter means large bronchial arteries as the chief source of blood to the lungs. Such atypical findings warrant a guarded prognosis. Tricuspid atresia differs from the tetralogy of Fallot in two respects only: (1) evidence of left ventricular enlargement and an absent or small right ventricle on roentgenography and fluoroscopy; (2) left axis deviation instead of right axis deviation in the electrocardiogram. Surgical results are equally good.

FROM THE AUTHORS' SUMMARY.

SOCIAL ADJUSTMENT OF SIX PATIENTS WITH HEMOPHILIA PRIOR TO AND DURING PROPHYLACTIC TREATMENT. ETHEL COHEN and ROSALIND L. HERRMANN, Pediatrics **3**:588 (May) 1949.

A study has been made of 6 patients treated for hemophilia by repeated frequent infusions of plasma. Prior to the start of treatment these patients were semi-invalids, hospitalized frequently for periods of weeks and months and handicapped in their adjustment to normal social life. Since treatment, they and their families have gained a feeling of confidence, without the fear of hemorrhage "hanging over their heads." They know that if a hemorrhage occurs, it probably will not incapacitate the patient, and that if it does the period of incapacitation will be comparatively short. Our observations indicate great improvement in the lives of the patients studied. They have acquired a new outlook on life and many positive experiences. From this study some insight has also been gained into the social component of this disease and into the problems both solved and created by effective treatment.

FROM THE AUTHORS' SUMMARY.

ANOMALOUS CHANNEL BETWEEN AORTA AND RIGHT VENTRICLE: REPORT OF A CASE. RICHARD C. BROWN and JOHN D. BURNETT, Pediatrics **3**:597 (May) 1949.

This is the case history of a 13 month old boy, on whom cardiac studies over a seven month period had suggested the presence of a large ductus arteriosus and

who died of purulent tracheobronchitis. Autopsy revealed an insignificant patent ductus and an unique vascular artery in the left posterior sinus of Valsalva, which passed into a small side chamber of the right ventricle, along the border of the pulmonary conus. This case exemplifies a group of cardiovascular anomalies which resemble a patent ductus arteriosus clinically and which may be treated surgically as such. A review of the literature, with a discussion on the various theories of the embryologic development, is given. The diagnostic criteria and the help which cardiac catheterization might give in confirming the diagnosis are indicated.

FROM THE AUTHORS' SUMMARY.

PENICILLIN, STREPTOMYCIN, DICUMAROL AND BLOOD COAGULATION: THROMBOPLASTIC PROPERTIES OF PENICILLIN. DAVID I. MACHT, South. M. J. **41**:720 (Aug.) 1948.

Laboratory studies showed that penicillin shortens the coagulation time of whole blood, as well as the prothrombin time. This was demonstrated to be true in patients as well. Amorphous penicillin seems to be more effective than the crystalline preparations, because of the various penicillin fractions which vary in their thromboplastic strength. The author states that the thromboplastic effects of penicillin and the anticoagulant effects of dicumarol are mutually antagonistic.

LOGAN, Rochester, Minn.

AZOTAEMIA IN INFANCY. S. A. DOXIADIS, Arch. Dis. Childhood **23**:55 (March) 1948.

A study was undertaken of 47 sick infants presenting blood urea values of 50 to 500 mg. per hundred cubic centimeters. An attempt was made to define the nature of the azotemia and the conditions under which it may develop. This azotemia is always extrarenal at the beginning, and the basic condition necessary for its development is dehydration due to a variety of causes. Contributory factors which may determine the degree of azotemia are the amount of protein intake, the concentrating capacity of the kidney and, to a lesser degree, the increased breakdown of tissue protein due to infection or starvation. Persistence of high blood urea values in spite of rehydration is of poor prognostic significance, as it indicates the development of irreversible changes in the renal tubules.

KELLY, Milwaukee.

COMPLETE HEART BLOCK IN CHILDREN. NORMAN S. CLARK, Arch. Dis. Childhood **23**:162 (Sept.) 1948.

Three young children with complete heart block are reported on. One child had frequent Stokes-Adams attacks and died two years after the onset of the heart block. The other 2 children, a brother and a sister, had no symptoms directly referable to the heart block and were alive and well nine months after the block developed.

It is suggested that in all 3 children the heart block was the result of measles, but the possibility that rheumatic carditis and some familial weakness of the conducting tissues may have played a part in the causation in 2 of the patients is admitted.

KELLY, Milwaukee.

ISOLATED (FIEDLER'S) MYOCARDITIS. H. EVERLEY JONES and A. G. MARSHALL, Arch. Dis. Childhood **23**:204 (Sept.) 1948.

A fatal case of idiopathic (Fiedler's) myocarditis is described. The diagnosis of the condition is discussed, and the importance of thorough histologic examination of the myocardium in young persons who die of unexplained cardiac failure is stressed.

KELLY, Milwaukee.

CONGENITAL HEART DISEASE. A. RAE GILCHRIST, Edinburgh M. J. **55**:385 (July) 1948.

The clinician is concerned more with altered function than with detached pathologic changes. A case in point is congenital heart disease in which a proper understanding of circulatory dynamics is essential to accurate diagnosis. With such basic knowledge as a background, the physician may approach the various diagnostic procedures with some assurance of success. In addition to careful physical examination, the judicious use of roentgenology and fluoroscopy is extremely important.

Gilchrist discusses, in some detail, the diagnosis of patent ductus arteriosus, ventricular septal defect, auricular septal defect, coarctation of the aorta and disorders in the cyanosed child. Taussig and Blalock and others have contributed greatly to the recognition and surgical treatment of several of these congenital defects. The author cites Taussig in that the conditions of about 60 per cent of cyanotic children over 2 years of age are operable and of these children 55 per cent are afflicted with Fallot's tetralogy.

MACDONALD, Pittsburgh.

THE HEMOLYSIS OF ERYTHROCYTES IN SODIUM CHLORIDE SOLUTION AND IN SODIUM PHOSPHATE BUFFERS. EDWARD B. HENDRY, Edinburgh M. J. **55**:427 (July) 1948.

Hendry discusses several of the factors involved in the measurement of hemolysis of erythrocytes in solutions of sodium chloride of varying concentrations. In addition, he has investigated hemolysis in iso-osmotic sodium phosphate buffer solutions. He observed in these that, at constant osmotic pressure, hemolysis depended on the p_H. Maximum hemolysis occurred at a p_H of 6.75 to 6.85. Oxygenation of the blood did not affect hemolysis at a constant osmotic pressure, but lowering the temperature increased the degree of hemolysis.

MACDONALD, Pittsburgh.

COARCTATION OF THE AORTA IN THE NEONATAL PERIOD. C. W. KESSON, Proc. Roy. Soc. Med. **41**:449 (July) 1948.

The baby was apparently normal until he was 4 days old, when cyanosis developed on crying. Forcible pulsation was observed in the neck and also in both brachial and axillary arteries. The blood pressure, which was equal in the two arms, measured 125 systolic and 90 diastolic. Blood pressure in the legs could not be determined, and no pulsation could be detected in the femoral artery. There was cardiac enlargement.

A roentgenogram of the chest showed the heart filling three fourths of the thorax and no notching of the ribs.

Notes on the autopsy and comment, in which the author states what other authorities consider the cardinal clinical features in coarctation of the aorta, conclude the report.

WILLIAMSON, New Orleans, La.

THE EFFECT OF SALICYLATE THERAPY ON QUICK'S TEST IN CHILDREN. M. ORLANDELLI, Clin. pediat. **30**:634 (Oct.) 1948.

Sodium salicylate causes a diminution in the prothrombin of the blood in both normal and rheumatic children, as measured by Quick's test. The giving of moderate doses of vitamin K will prevent this diminution from taking place. This finding is probably explicable on the basis of chemical antagonism between the two drugs, which may affect a specific hepatic function.

HIGGINS, Boston.

DIAGNOSIS OF COARCTATION OF THE AORTA IN CHILDREN. J. I. DE BRUYNE, S. VAN CREVELD and H. A. P. HARTOG, Nederl. tijdschr. v. geneesk. **92**:3636 (Nov. 6) 1948.

Coarctation of the aorta, its diagnosis, differential diagnosis, complications, prognosis and indications for operation, are discussed, with a description of 8 cases. Operation in 1 of these cases showed a constriction of the aorta of 4 cm.; in the middle of the stenotic part was the entrance of the open ductus arteriosus. It was impossible to make an end to end anastomosis of the portions of the aorta below and above the stenosis; so the left subclavian artery was fastened end to end to the distal part of the aorta. The boy recovered.

The roentgenogram of a boy 5 years of age already showed notching of the ribs.

At present no general criteria can be given as an indication for operation. Beginning enlargement of the heart and intermittent claudication in young persons who do not show symptoms of a complicating heart disorder are a reason for surgical treatment.

FROM THE AUTHORS' SUMMARY.

Diseases of Nose, Throat and Ear

ACUTE SINUSITIS IN CHILDREN. GLEN J. GREENWOOD, Illinois M. J. **91**:313 (June) 1947.

A review of the embryologic, anatomic, physiologic and etiologic factors and symptomatology, therapy and prognosis of acute sinusitis in children is given. There is too much detail in the article to permit an adequate abstract.

BARBOUR, Peoria, Ill.

GROUP PURE TONE HEARING TESTING IN THE PUBLIC SCHOOLS. HAYES A. NEWBY, J. Speech Disorders **12**:357 (Dec.) 1947.

A new group pure tone hearing test was administered to 1,200 subjects from the twelfth through the second grades. Experimental testing was conducted with samples of the population from the eighth through the second grades to study the reliability and validity of this test and its efficiency as a screening device. The results were as follows:

1. Ninety per cent of the ears showed differences from results on group test or group retest at the frequencies tested of 5 decibels or less.

2. For the entire group of 188 ears in the validity studies from the eighth through the third grades almost 90 per cent of the ears showed differences from the results on group test to those on individual tests at the frequencies tested of 10 decibels or less.

3. The group pure tone test operates most efficiently as a screening device when a significant loss of hearing on the group test is defined as a loss of 20 decibels or more for any frequency for either ear.

4. Use of the 20 decibel loss as the significant criterion results in a correct classification for 80 per cent of the ears, the needless retesting of 18.6 per cent of the ears and the failure to discover 1.6 per cent of the ears which actually have significant losses.

5. On the basis of this study the group pure tone test appears to be superior to the group phonograph speech audiometer test as an efficient screening device.

PALMER, Wichita, Kan.

REHABILITATION OF THE AURALLY HANDICAPPED THROUGH THE STUDY OF SPEECH READING IN LIFE SITUATIONS. BORIS V. MORKOVIN, J. Speech Disorders **12**:363 (Dec.) 1947.

The stress in training for speech reading should be put on the complete stimulus pattern rather than on the movements of the lips or other single items. Speech reading is most successful when it is taught on the basis of life problems and the necessity for solving them. All the senses are interlocked in their modalities and successful teaching is done by audiovisual kinesthetic cooperation. Motion picture films are helpful in teaching speech reading. Two illustrative cases are presented.

PALMER, Wichita, Kan.

SUGGESTIONS FOR SUPERVISED TEACHING IN SPEECH CORRECTION. ELIZABETH C. MACLEARIE, J. Speech Disorders **12**:369 (Dec.) 1947.

This is a review of the special situation met by speech correctionists who plan to teach in the public schools and a description of the various items necessary for a student to learn prior to going into the public school situation.

PALMER, Wichita, Kan.

A PROGRAM FOR THE SPEECH-INHIBITED CHILD. AMY BISHOP CHAPIN and MARGARET CORCORAN, J. Speech Disorders **12**:373 (Dec.) 1947.

The term "delayed speech" has been used too often to include all kinds of immature speech development. Children accepted for this study were screened by excluding the mentally deficient, autistic, prepsychotic children, cretins, mongoloids and mentally deteriorated patients and those with gross brain damage. The children selected, therefore, showed evidence of normal, intelligent behavior, passed all neuropsychiatric examinations with a diagnosis of some form of emotional-environmental retardation or suspected aphasia. Sixteen children were involved in the study at an average age of 5.2 years. The nursery school situation made it possible to overcome fears and feelings of inadequacy and to develop social adequacy. Speech was stimulated carefully. Each child was addressed as though he were expected to talk. Much work was done with the parents, explaining the problems involved by lecture and individual conference. Of the 16 children, 12 were either dismissed as having obtained normal speech for their age level or accepted at regular schools. Two needs were discovered in this study: first, the need for an adequate pamphlet for parents and, second, the need for reliable diagnostic procedures. The authors state that 45 per cent of the children with so-called delayed speech referred to the clinic in a six month period were not deaf, feebleminded, suffering from endocrine imbalance, autistic or prepsychotic but merely speech-inhibited normal children.

PALMER, Wichita, Kan.

VISUAL AIDS TO SPEECH IMPROVEMENT. WILBERT PRONOVOST, J. Speech Disorders **12**:387 (Dec.) 1947.

Use of the oscilloscope for showing differences in rate, duration and pitch in speech is described. The oscilloscope is also used in some types of work with defective voices in which too large a crescendo occurs, as in the "glottal attack." The voltmeter and similar devices are useful in regulating volume. An apparatus which will measure nasality directly by activation of an amplifier is mentioned, and a speech game for children in which letters are mounted behind a bulb system with nine windows is discussed.

PALMER, Wichita, Kan.

AN EXPERIMENTAL PROGRAM FOR HARD OF HEARING CHILDREN. D. E. MORLEY, J. Speech & Hearing Disorders **13**:337 (Dec) 1948.

Hearing aids and a six weeks' summer program of instruction in acoustic training, lip reading, speech and correlated activities were provided for a group of hard of hearing children for whom no further medical treatment was indicated and for whom no special class facilities were available. Acoustic examinations were made prior to the program at the time of selection of the hearing aids at the conclusion of the training program and approximately six months later. Tests of achievement, general ability and personality and social adjustment were made during the program and approximately six months later. The observable results or trends in this project were obtained from a comparison of each child's own responses, development or changes as recorded on the first tests and on the retests. Supplementary information was received from the parents of the children.

PALMER, Wichita, Kan.

AUDIOMETRIC TESTS OF SPEECH DEFECTIVE COLLEGE STUDENTS. INEZ E. HEGARTY and VIRGINIA R. MILLER, J. Speech & Hearing Disorders **13**:361 (Dec.) 1948.

One hundred and eighteen women students enrolled in the speech clinic at Wellesley College during the year 1946-1947 were given audiometric tests. The majority of students had hearing within normal limits. The hearing of 14 per cent was normal in the right ear, with some loss in the left. That of 14 per cent was normal in the left ear, with some loss in the right. Eighteen per cent showed some loss in both ears. Four per cent had subnormal hearing in one or both ears. If 20 decibels is used as the norm, 81.4 per cent had normal hearing in both ears, 14.4 per cent showed some deviation in one or both ears and 4.2 per cent had subnormal hearing in one or both ears. The authors urge that a routine hearing conservation program is necessary.

PALMER, Wichita, Kan.

PARENT PARTICIPATION IN TEACHING SPEECH TO THE DEAF CHILD. GRACE HARRIS LASSMAN, J. Speech & Hearing Disorders **13**:366 (Dec.) 1948.

The author urges that a complete teacher-training program is not absolutely necessary for parents, but greater scope for parental participation in all the areas of education of the young deaf child would permit the teacher to reach more children and to do better work with the children seen.

PALMER, Wichita, Kan.

CONTROL OF POST-TONSILLECTOMY AND POST-ADENOIDECTOMY HEMORRHAGE BY DOUBLE-STRENGTH POSTERIOR PITUITARY SOLUTION. J. W. McLAURIN, Laryngoscope **58**:1315 (Dec.) 1948.

Bleeding following tonsillectomy and adenoidectomy was controlled successfully in 103 of 105 cases by the use of posterior pituitary injection U. S. P., double strength. Side reactions were not serious.

The solution should not be used if the patient has heart disease, because of the decrease of flow in the coronary vessels.

HITSCHLER, Philadelphia [Arch. Otolaryng.].

VINCENT'S ANGINA—TREATMENT WITH PENCILLIN BY ATOMIZER. A. E. FISHMAN, Med. Rec. **161**:356 (June-July) 1948.

A simple and pleasant method of local administration of penicillin to buccal mucous membrane for the treatment of Vincent's angina is described. A solution of 100,000 units to 30 cc. of distilled water or isotonic sodium chloride solution is sprayed into the mouth and on the gums by ordinary atomizer every two hours. Twenty patients were treated, of whom only 4 required treatment longer than four days for complete recovery. The described method is particularly advantageous for use in children because of the ease of administration as compared with topical application, mouth washes, injections and lozenges.

FERDINAND, Peoria, Ill.

INFECTIOUS CROUP: II. "VIRUS" CROUP. EDWARD F. RABE, Pediatrics **2**:415 (Oct.) 1948.

So-called virus or nonbacterial croup occurred in 87 per cent of 347 cases of infectious croup. The pathologic changes of the disease are distinct from those of croup due to Hemophilus influenzae type B or Corynebacterium diphtheriae. Clincally, "virus" croup is a progressive disease, with downward spread of the infection in the respiratory tract. The inflammation can extend to various regions resulting in the clinical forms of the disease known as laryngitis, laryngotracheitis or laryngotracheopneumonitis. The mortality rate increases as the disease spreads downward.

There is no well founded specific treatment for "virus" croup. However, sulfadiazine should be given to all patients with infectious croup until cultures of material from rhinopharynx and of blood assure the absence of potential pathogens. Continued chemotherapy should be given all patients severely ill with the disease.

The most frequent severe complication of "virus" croup is some form of extra-alveolar intrathoracic air. The commonest cause of death is respiratory embarrassment.

FROM THE AUTHOR'S SUMMARY.

INFECTIOUS CROUP: III. HEMOPHILUS INFLUENZAE TYPE B CROUP. EDWARD F. RABE, Pediatrics **2**:599 (Nov.) 1948.

Croup due to Hemophilus influenzae type B occurred in 8 per cent of a group of 347 cases of infectious croup. Bacteriologically and pathologically, the disease was distinct from diphtheritic and so-called virus croup. The endoscopic picture was that of extreme supraglottic swelling and epiglottitis. Clinically, the disease was characterized by the following symptoms: brief antecedent history of severe sore throat, sudden onset and rapidly progressive signs of croup, tender cervical adenitis, evidence of laryngitis and severe epiglottitis, leukocytosis and signs of

shock out of proportion to the duration of illness. Treatment consisted of two parts: (1) relief of the supraglottic obstruction by tracheotomy, and (2) combating the bacteremia and toxemia with administration of sulfonamide drugs, type-specific rabbit antiserum and transfusions. Death from this disease was attributed to bacteremia and toxemia, aided by progressive obstruction of the respiratory tract. The over-all case fatality for this form of croup was 18 per cent, the range being 7 per cent for laryngitis to 40 per cent for laryngotracheopneumonitis.

FROM THE AUTHOR'S SUMMARY.

ROENTGEN TREATMENT OF SUBACUTE SINUSITIS IN CHILDREN. DONALD R. LAING, Radiology **50**:52 (Jan.) 1948.

Of 4,000 children treated in a two year period, 900 were listed as having subacute sinusitis. Roentgenograms showed a varying degree of infection in the maxillary or ethmoid sinuses. The beginning dose to blocked antral sinuses was usually 30 r. In the average child, the treatment was given anteroposteriorly with a port of 8 to 10 cm. protecting the eyes with lead. Other ports were occasionally used but never more than three in any one case. Roentgen factors for younger children were 130 kilovolts primary radiation, 5 milliamperes; 3 mm. of aluminum filtration, 4.1 mm. aluminum half-value layer and 30 cm. of distance. Factors for older children were 140 kilovolts primary radiation, 5 milliamperes; 0.25 mm. of copper and 1 mm. of aluminum filtration, 0.42 mm. copper half-value layer and 30 cm. of distance. These treatments were administered for eight days and a total of 240 r was given to each area. Seventy-one per cent were cured after one series of roentgen treatments; 15 per cent showed moderate improvement; 55 per cent with recurrences had complete clearance after a second series of treatments.

ANSPACH, Chicago.

CONGENITAL ATRESIA OF THE NASOLACHRYMAL DUCT. NICHOLAS W. WOYWITKA, Canad. M. A. J. **59**:357 (Oct.) 1948.

A genealogic tree showing the occurrence of congenital atresia of the nasolacrimal duct over five generations is presented. Nine of 46 members of the family were afflicted. The question of penetrance of the dominant gene is commented on.

MCGUIGAN, Evanston, Ill.

THE TREATMENT OF CHRONIC SINUSITIS IN CHILDREN. VERNON DE BOISSIÈRE, Canad. M. A. J. **60**:14 (Jan.) 1949.

The author presents a brief discussion of chronic sinusitis in children. He advocates the use of roentgen therapy, with displacement by penicillin his second choice.

MCGUIGAN, Evanston, Ill.

ROENTGEN THERAPY FOR SUBGLOTTIC LARYNGITIS IN CHILDREN. J. MARINONI and E. FRACASSO, Clin. pediat. **30**:247 (April) 1948.

Thirteen children with subglottic laryngitis were treated by roentgen irradiation. Excellent results were obtained in 2 of the 3 children who still showed constriction two to three weeks following tracheotomy. Good results were obtained with the treatment of 5 children with acute laryngitis (1 with the severe disease and 4 with the mild form). Only 1 of 4 children with subacute laryngitis obtained any relief from the treatments, and 1 child having the chronic disease with acute exacerbations was not benefited. It was apparent that the earlier in the disease the roentgen treatment was given, the better the chance for relief of the condition.

No serious difficulty was encountered from an immediate edema of the larynx following the irradiation; however, small initial doses are recommended for children without tracheotomy tubes.

HIGGINS, Boston.

ROENTGEN TREATMENT OF WALDEYER'S TONSILLAR RING IN CHILDREN. D. CIRILLO, Lattante **19**:327 (June) 1948.

Over a period of twelve years, roentgen irradiation of the tonsillar tissue was given to 435 children; follow-up reports were obtained on 206 of them. Favorable therapeutic results followed the irradiation in 90 per cent, and no benefit was noted in 10 per cent of the children. In no child was there any injury referable to the treatment.

HIGGINS, Boston.

Diseases of Lungs, Pleura and Mediastinum

EMPYEMA THORACIS IN INFANTS AND CHILDREN. ALFRED E. CHAPLIN, Arch. Dis. Childhood **22**:91 (June) 1947.

An analysis of 275 cases of empyema in children and infants is made with regard to age, mortality and bacteriologic data. Results of two five year periods, one of "nonsulfonamide" and the other of "sulfonamide" therapy, are compared. The value of sulfonamides in the prevention of postpneumonic empyema is assessed. The resistance of staphylococcic diseases to sulfonamide is shown.

The use of penicillin in the treatment of sulfonamide-resistant pneumonia and of empyema due to sensitive organisms is reviewed.

A collected series of 21 cases of penicillin-treated empyema in children and infants is presented. Good results are reported with 1 death in the entire series. The limitations of treatment of acute empyema in children and infants by aspiration and penicillin alone are discussed. The need for surgical drainage in many cases is shown.

KELLY, Milwaukee.

A SHORT HISTORY OF THE PNEUMOCOCCUS WITH SPECIAL REFERENCE TO LOBAR PNEUMONIA. J. T. SMEALL, Edinburgh M. J. **55**:129 (March) 1948.

In 1881, Sternberg and Pasteur simultaneously reported lance-shaped diplococci in saliva capable of producing septicemia in rabbits. There is no doubt that these organisms were pneumococci. In the same year Eberth demonstrated diplococci in pathologic material from a case of pneumonia but was unable to explain their significance. Talamon, Friedländer and Gram contributed to the search, but it was Weichselbaum and Fränkel who independently, in 1886, demonstrated that the Pneumococcus is the cause of pneumonia in the majority of cases.

Milestones in the history of the organism are as follows: 1891, the Klemperers first demonstrated the curative effects of immune rabbit serum; 1912, Neufeld and Haendel divided pneumococci into three types; 1917, Dochez and Avery discovered the type specificity of capsular polysaccharide; 1932, Cooper and her associates distinguished thirty-two types of pneumococci. In 1944, Eddy listed seventy-five types of pneumococci. There are probably more.

MACDONALD, Pittsburgh.

FACTORS LEADING TO THE PRODUCTION OF BRONCHIECTASIS IN CHILDHOOD, and ITS PREVENTION. A. PALLEY, South African M. J. **22**:169 (March 13) 1948.

A brief discussion of the physiologic causes of bronchiectasis is presented, with a description of the pathologic factors involved. Prevention of the disease is urged

through careful treatment of the acute infection, breathing exercises and early ambulation, general attention to hygiene and thorough and early follow-up study of patients presenting suggestive signs.

McGUIGAN, Evanston, Ill.

NONTUBERCULOUS SEROFIBRINOUS PLEURISY. E. P. BOCCOLI, Clin. pediat. **30**:264 (April) 1948.

A case report is given of a boy 11 months of age who had pleurisy with effusion after a ten day illness, during which a sulfonamide drug was given. The effusion fluid was sterile, and Rivalta's reaction was positive. Intradermal tuberculin gave negative reactions. The condition is analogous to the metapneumonic pleurisy described by Schiassi in adults.

HIGGINS, Boston.

DAILY RHYTHM OF RESPIRATION IN INFANTS. C. IMPERATO and L. LANDUCCI, Lattante **19**:353 (June) 1948.

The mean respiratory rate of newborn infants was observed to be 55, of infants 1 to 6 months old 46.5, of infants 6 to 12 months old 33 and of children 2 to 3 years old 30. The lowest respiratory rate was observed between 3 and 6 a.m. and the highest rate at 9 p.m.

HIGGINS, Boston.

STATISTICAL AND CLINICAL ASPECTS OF PURULENT PLEURISY IN INFANCY OVER FIFTEEN YEARS. UMBERTO GIURANNA and CARMINE MELINO, Pediatria **56**:48 (Jan.-March) 1948.

Statistical and clinical investigations carried out in the span of fifteen years (1931 to 1947) led the authors to stress the diminished morbidity in purulent pleurisy during infancy in recent years due to the application of sulfonamide therapy in acute disorders of the respiratory tract. Furthermore, the authors point out that, while no changes have been observed in incidence according to age, sex, season and localization in regard to the etiologic agent in the two periods 1931 to 1938, before the introduction of sulfonamides and 1940 to 1947, after the introduction of sulfonamides, an increase in the number of staphylococcic forms as compared with pneumococcic forms has been observed. So far as mortality is concerned, there is no evidence of a perceptible diminution in those years sulfonamide drugs were used (1940 to 1947) as compared with the previous period (1931 to 1938), whereas the use of penicillin in the last two years has seemed to prove more successful.

FROM THE AUTHORS' SUMMARY.

ENDOPLEURAL TREATMENT OF ACUTE PULMONARY INFECTIONS AND OF HILAR AND MEDIASTINAL TUBERCULOUS ADENITIS WITH PENICILLIN, STREPTOMYCIN AND POLYLYSATES. G. TACCONE, Pediatria **56**:207 (April) 1948.

The polylysates are prepared by the method of Zironi and consist of a colloidal suspension of polypeptides of low molecular weight and a small amount of amino acids. Successful results followed the endopleural administration of streptomycin and polylysates to patients with pleural effusions. The endopleural route is also recommended in the treatment of tuberculous hilar adenitis with streptomycin and of other pulmonary infections with penicillin.

HIGGINS, Boston.

PLEURAL EMPYEMA IN CHILDREN TREATED SUCCESSFULLY WITH PENICILLIN. TEA OBERHOFER-ŠIK, Ann. pædiat. **170**:200 (April) 1948.

An important change was brought about in the treatment of pleural empyema in children by the advent of penicillin for the following reasons:

1. The mortality from pleural empyema in infants and small children decreased rapidly. Of 33 affected children in this series 29 were cured with penicillin.

2. The duration of the illness was considerably shortened. While previously, in the few rare children who recovered, cure took several months, after the use of penicillin, the majority of the patients were cured in about a fortnight.

3. Pleural empyema, if treated with penicillin, disappears without sequelae, such as residual cavities and deformities of the thorax, and without the formation of thick pleural adhesions, as was demonstrated in a patient in the course of a postmortem examination.

4. From the economic point of view the reduction in the number of the days of illness is important.

FROM THE AUTHOR'S SUMMARY.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

CHOLEDOCHUS CYST. CHARLES E. DAVIS JR., Ann. Surg. **128**:240 (Aug.) 1948.

The author reports a case of choledochus cyst occurring in a 5 year old boy. The condition was diagnosed before operation and was apparently treated successfully by choledochocystoduodenostomy. The author comments briefly on the rarity of the condition and its historical aspects.

BANTIN, Omaha.

REDUCTION OF INTUSSUSCEPTION BY BARIUM ENEMA. MARK M. RAVITCH and ROBERT M. MCCUNE JR., Ann. Surg. **128**:904 (Nov.) 1948.

According to the authors, the cumulative experience of seventy-five years in the treatment of intussusception shows reduction by hydrostatic pressure to be a safer primary approach than operation.

The authors' barium sulfate technic is as follows: As soon as the presumptive diagnosis of intussusception is made, the child is taken to the fluoroscopic room and the staff of the operating room is alerted. Without the induction of anesthesia, an unlubricated Foley bag catheter is inserted in the rectum. The bag is distended with 20 to 40 cc. of air, and barium sulfate is permitted to run in from a height of 3 feet (91 cm.). The barium sulfate usually runs rapidly to the intussusception, which it outlines, producing a concave meniscus. The ends of the meniscus extend proximally until suddenly the intussusception gives ground. If complete reduction is not achieved, the child is permitted to expel the enema and two more attempts are made. If the third injection of barium sulfate is unsuccessful, operation is performed.

After reduction, powdered charcoal is instilled in the stomach. A successful reduction is denoted by the following criteria: 1. The barium sulfate enters well into the small bowel. 2. At times, the child returns the barium sulfate with feces or flatus, proof in acute intussusception that the obstruction is relieved. 3. The mass is no longer palpable. 4. The child is clinically relieved. 5. Charcoal given by mouth is subsequently recovered in the stool.

The authors discuss the reasons for resistance among surgeons to this treatment.

BANTIN, Omaha.

THE ROLE OF BILE IN THE ABSORPTION OF STEROID HORMONES FROM THE GASTRO-INTESTINAL TRACT. M. M. HOFFMAN, G. MASSON and M. L. DESBARATS, Endocrinology **42**:279 (April) 1948.

Since bile is required for the optimum absorption of cholesterol from the gastrointestinal tract, it has been assumed that bile is also essential for the enteral absorption of steroid hormones and related substances. The experiments reported in this article indicate that dehydroisoandrosterone, progesterone and desoxycorticosterone acetate can be absorbed from the gastrointestinal tract of the rabbit in the absence of bile.

JACOBSEN, Buffalo.

LIVER DAMAGE AND GROWTH IN THE RABBIT. EDWARD J. THACKER and GORDON H. ELLIS, J. Nutrition **36**:579 (Nov. 10) 1948.

Thacker and Ellis found that a diet of whole milk powder (fortified with manganese, copper, iron and iodine) is inadequate for the rabbit, as it resulted in subnormal growth and fatty and cirrhotic livers. To prevent hepatic damage, large amounts (50 per cent) of dehydrated alfalfa meal were needed, while only small amounts (1 per cent) were needed to stimulate the growth rate. Their experiments indicated that milk does not contain a toxic factor responsible for these results, and that the results were not due to the lack of roughage, of any of the known fat-soluble and water-soluble vitamins or of the labile methyl groups. Purified diets, when supplemented with a complete vitamin mixture, offered no protection against hepatic damage but when supplemented with yeast offered partial protection. Crude casein produced better growth than purified casein.

FREDEEN, Kansas City, Mo.

INVESTIGATION OF SOME NEWER SULFONAMIDES AS INTESTINAL CHEMOTHERAPEUTIC AGENTS. H. J. FLORESTANO and M. E. BAHLER, J. Pharmacol. & Exper. Therap. **92**:196, 1948.

Studies were made on the blood concentration and bactericidal action (on coli organisms) of the newer sulfonamide drugs given orally. Of the group studied succinylsulfathiazole seemed to be the most satisfactory in that it was "highly active in the intestinal tract of mice and dogs and only slightly absorbed into the blood." The authors, therefore, recommend it for clinical trial.

PILCHER, Cleveland.

THE EFFECT OF CENTRAL NERVOUS SYSTEM DEPRESSANTS ON THE EMPTYING TIME OF THE HUMAN STOMACH. DAVID W. NORTHUP and EDWARD J. VAN LIERE, J. Pharmacol. & Exper. Therap. **93**:208 (May-Aug.) 1948.

In a paper previously published from this laboratory it was shown that amobarbital sodium N. N. R. (amytal sodium®) produced a decrease in the emptying time of the human stomach, as determined fluoroscopically with a farina test meal to which barium sulfate was added. The present study is a continuation of the work on medical students with the use of other narcotic drugs, chloral hydrate, bromisovalum N. N. R. (bromural®), pentobarbital sodium and paraldehyde, and the conclusions were as follows: Consistently increased motility was observed only with the use of pentobarbital sodium, indicating that sedation is not the principal factor responsible for the decreased emptying time seen after administration of certain central nervous system depressants (barbiturates).

PILCHER, Cleveland.

INTUSSUSCEPTION IN CHILDHOOD. ROBERT E. GROSS and PAUL F. WARE, New England J. Med. **239**:645 (Oct. 28) 1948.

A series of 610 cases of intussusception treated at the Children's Hospital in Boston is presented. The causation in 95 per cent of the cases was unknown. Intussusception is characterized by sudden onset of paroxysmal abdominal pain, vomiting, bloody stools and a palpable abdominal mass, the condition occurring usually in a well nourished baby. Roentgenologic examination with the use of a barium sulfate enema may aid in making the diagnosis in atypical cases, but it is not necessary in the majority, in which the history and physical findings are sufficient to establish the proper diagnosis.

The optimum treatment of intussusception is by surgical reduction after rapid but important preoperative preparation. If resection is necessary, exteriorization is the method of choice, since this rigidly prevents contamination or soiling of the peritoneal cavity. Postoperative care includes the use of gastric suction, transfusion of blood or plasma, infusion of dextrose or saline solution and, in some cases, institution of chemotherapy and placement of the child in a high concentration oxygen tent.

The mortality rates for intussusception have improved steadily; in the last few years the mortality has been reduced to 2.7 per cent.

FROM THE AUTHORS' SUMMARY.

EXPERIMENTAL ENTEROCOCCAL FOOD POISONING IN MAN. A. G. OSLER, L. BUCHBINDER and G. I. STEFFEN, Proc. Soc. Exper. Biol. & Med. **67**:456 (April) 1948.

Attempts at feeding 70 kittens with evaporated milk containing cultures of Streptococcus faecalis (twenty hour) to produce effects of food poisoning were without significance. Likewise, no special changes resulted when the milk was fed to 21 human subjects. Later four different strains of Str. faecalis, five hour cultures, were added to egg salad, custard and sterile milk given to 26 human subjects. Acute gastric or intestinal symptoms developed in one fourth of them. The authors conclude that their observations tend to confirm the etiologic role of this organism in naturally occurring outbreaks of food poisoning.

HANSEN, Galveston, Texas.

OBSTRUCTION OF THE ALIMENTARY TRACT IN INFANCY. WILLIAM A. EVANS JR., Radiology **51**:23 (July) 1948.

The roentgenologic diagnosis of various obstructions observed in 400 infants at Children's Hospital of Michigan, Detroit, is discussed and illustrative roentgenograms are generously furnished. Hypertrophic pyloric stenosis made up 50 per cent, intussusception 20 per cent and the atresias 16 per cent of the obstructions. Incidence of other conditions varied from 2 to 8 per cent each.

ANSPACH, Chicago.

FIBROCYSTIC DISEASE OF THE PANCREAS. LOWELL S. GOIN, Radiology **51**:36 (July) 1948.

Children with this disease seem to fall into three groups: (1) those who die soon after birth with meconium ileus, intestinal stenosis or atresia; (2) those displaying lesions of the gastrointestinal and respiratory tracts in their first year

of life, who usually die of respiratory infections, and (3) those who present the signs and symptoms of celiac-like disease, associated with bronchitis and bronchiectasis.

Roentgenograms of the chest show segmented and patchy atelectasis and emphysema, hilar thickening and bronchopneumonia. The appearance on the roentgenograms should suggest the possibility of pancreatic fibrocystic disease, and thereafter the diagnosis may be thoroughly established. This disease may account for as much as 4 per cent of deaths in infancy.

ANSPACH, Chicago.

MESENTERIC LIPOMA IN A CHILD: ROENTGENOLOGIC VISUALIZATION. JOSEPH SELMAN and JOHN R. BENDER, Radiology **51**:66 (July) 1948.

The greater translucency of intra-abdominal lipomas in roentgenograms may lead to the proper diagnosis, but other fat-containing tumors present a similar shadow, namely, dermoids, fibromyxoliposarcomas and liposarcomas. If the lipoma contains calcifications, the differential diagnosis between it and dermoids becomes more difficult, as was the case in the 4 year old girl reported on. The tumor presented an area of lessened density occupying the central portion of the abdomen and greatly displacing other structures. The published roentgenograms reveal that the shadow was less transparent than the gas in the colon but of greater density than the liver. A lipoma the size of a grapefruit was removed and observed to contain particles of calcification.

Reports of lipomas in the mesentery of children are rare in the literature. The author's case is the fourth such condition reported in a child.

ANSPACH, Chicago.

A CASE OF INTUSSUSCEPTION. J. A. M. CAMERON, Canad. M. A. J. **59**:568 (Dec.) 1948.

A case is described of a colic intussusception due to a solitary adenoma of the sigmoid mucosa. The condition was cured by removal of the tumor rectally.

McGUIGAN, Evanston, Ill.

ETIOLOGICAL ASPECTS OF GASTRO-ENTERITIS. E. HINDEN, Arch. Dis. Childhood **23**:38 (March) 1948.

"Diarrhea and enteritis in children under 2 years of age" is a heterogeneous group of gastroenteral complaints. Most of the severe types of this group belong to an acute infectious (probably specific) disorder, which carries a case mortality of 33 to 50 per cent. This disease occurs in definite small epidemics at different times in different places, but mainly in early winter. Congregation of susceptible children favors the development of an epidemic; so the disease is found, with increasing frequency, in overcrowded cities, in children's hospital wards and, particularly, in the nurseries of maternity hospitals. The pathogen is nonbacterial and may well be viral. The route of entry is not oral but probably respiratory. The brunt of the infection falls on the intestine, its regional lymph glands and the liver. The value of chemotherapy is doubtful, but blood transfusion seems to exert a specific effect. There is no good evidence that this disease is caused by parenteral infection. There is no good reason for considering "epidemic diarrhea of the newborn" a separate entity. This term merely describes what happens when severe gastroenteritis breaks out in a maternity nursery.

KELLY, Milwaukee.

CONGENITAL FIBROCYSTIC DISEASE OF THE PANCREAS: A REPORT OF TWO PROVED CASES OF DISSIMILAR CLINICAL TYPES IN SIBLINGS. AGNES R. MACGREGOR and KENNETH RHANEY, Arch. Dis. Childhood **23**:60 (March) 1948.

The occurrence of fibrocystic disease of the pancreas in siblings is reported. One died of respiratory infection at the age of 4 months and the other with meconium ileus at the age of 2 days. In both children the diagnosis was proved by observations at autopsy. The pathologic changes in the pancreas appeared to result from an abnormal secretion of the acinar cells. A similar abnormality was present in the bronchial mucous glands of the infant who died of respiratory infection.

KELLY, Milwaukee.

A CASE OF LYMPHOSARCOMA OF THE INTESTINE IN A CHILD. KATHERINE J. GUTHRIE, Arch. Dis. Childhood **23**:199 (Sept.) 1948.

A case of intestinal lymphosarcoma in a boy is described which proved fatal in six weeks from the clinical onset. At autopsy, widespread tumor growth was observed in the intestine, kidney, mesenteric glands and bones. Clinical symptoms of gastrointestinal or renal disease had been negligible.

The diagnosis of intestinal lymphosarcoma should be considered in a child with an abdominal tumor, accompanied with rapidly progressive loss of weight, pallor and lassitude.

KELLY, Milwaukee.

CONGENITAL ANOMALY OF THE LIVER. A. ANANTHANARAYANA AYER and M. THANGAVELU, J. Indian M. A. **17**:291 (June) 1948.

Autopsy on a 40 year old man revealed as an incidental observation an anomalous liver. The anomaly consisted of a large left lobe and a diminutive right lobe. There was extra lobulation of the left quadrate lobes similar to the fissuring of the fetal liver. A continuous cleavage line representing the fissure at the site of the gallbladder fossa was present. The condition appears to be evolutionally primitive and resembles that in the liver of an Old World monkey, Semnopithecus entellus.

MCGUIGAN, Evanston, Ill.

THE CELIAC SYNDROME. PETER VÉGHELYI, Paediat. danub. **1**:117 (Feb.) 1947.

The clinical picture presented by the various types of dystrophies listed as celiac disturbances is more or less uniform, although the pathogenesis is far from being so. Various causes may lead to the same final result, but larvated forms are also frequent.

The basis of the disturbance is that the fat ingested cannot be absorbed from the intestine and a great part of it is again excreted. Besides steatorrhea, the following symptoms may be present in all forms: (1) underdevelopment, so-called infantilism, with extreme wasting and abdominal distention; (2) anemia and its consequences, and (3) hypovitaminoses, such as rickets and hypoprothrombinemia. Secondary symptoms, appearing only in some of the forms, are diarrhea, osteoporosis, disturbances of the iron metabolism, disturbances of the water metabolism and endocrine dysfunctions.

Exclusion of bile from the intestine gives rise to steatorrhea. If, owing to cystic fibrosis or dysfunction of the pancreas, there is lack of lipase, development will be hindered and a hyperchromic anemia arise, but there is no demineralization and growth is seldom retarded. Various inflammations of the pancreas may result in deficient secretion. This deficiency frequently remains latent and mani-

fests itself only in wasting or retardation of development. Similar conditions arise when the pancreatic ducts are being obstructed, usually by tuberculous lymph nodes.

All the aforementioned symptoms may develop when the process of absorption itself is disturbed. In severe cases, absorption of carbohydrates, iron, salts and water is also affected. Apart from the genuine celiac disease, possibly caused by the deficiency of a factor of the vitamin B_2 complex, such conditions result from severe infection with Giardia lamblia, from deficiency of the adrenal cortical hormone, from extensive tuberculosis of the mesenteric lymph nodes or from intestinal lipodystrophy.

FROM THE AUTHOR'S ABSTRACT.

TRIBOULET'S TEST IN GASTROINTESTINAL DISEASES. P. VÉGHELYI, Paediat. danub. **1**:163 (March) 1947.

Examinations were made on 457 tuberculin-negative children in order to determine the value of the Triboulet reaction, which has often been recommended for the diagnosis of intestinal tuberculosis, in the differentiation of various disorders of the gastrointestinal tract. In its original form, the test was found to be unsatisfactory, but when a reading was made after three and one-half hours, the results were reliable.

Such a first reading was negative in nearly all the healthy children and in those who had diseases not involving the intestinal tract. In those with pneumonia, the subsequent readings were positive. The test is of value in the localization of intestinal hemorrhages, the result being negative when they occur above the jejunum, as, for instance, peptic ulcers. It proved reliable for the quick differentiation of bacillary dysenteries but had no value in the diagnosis of tuberculosis, because several other ulcerative processes, as typhoid, also gave positive results.

FROM THE AUTHOR'S ABSTRACT.

ABSORPTION OF SULFANILAMIDE, SULFAPYRIDINE AND SULFAMETHYLTHIAZOLE FROM THE RECTUM OF INFANTS. A. SASS-KORTSAK and J. SZÉNÁSY, Paediat. danub. **1**:341 (June) 1947.

Sulfamethylthiazole and sulfapyridine administered in suppositories are absorbed only to a small extent from the rectum of infants.

The absorption of sulfanilamide is somewhat better, but a blood level necessary for therapeutic purposes cannot be attained in this manner.

According to some observations, sulfathiazole seems to be more readily absorbed from the rectum when administered in solution than in suppositories and the absorption of such solutions is about equal to that of sulfanilamide from suppositories.

FROM THE AUTHORS' ABSTRACT.

CIRRHOSIS OF THE LIVER AND PATHOLOGIC CARBOHYDRATE METABOLISM. L. BARTA and Z. ERDÖS, Paediat. danub. **1**:357 (June) 1947.

In a girl 9 years of age cirrhosis followed epidemic hepatitis.

The condition took an unusually rapid course, leading to death in five months. Ascites developed in the last weeks.

The absence of the Staub-Traugott effect in a double tolerance test with galactose and dextrose is regarded as further proof that this phenomenon is linked with hepatic function. The examinations performed strengthened the supposition that the various functions of the liver are independent of each other. At a stage

when the assimilation of both dextrose and galactose was already impaired, glucose was still formed well. This was further proved by the normal curves for insulin and epinephrine tolerance.

The Staub-Traugott effect reappeared following administration of adrenal cortex extract, although the state of the patient remained unchanged. This shows that corticosterone has a favorable influence on the sugar metabolism of the liver.

FROM THE AUTHORS' ABSTRACT.

NOMA TREATED WITH PENICILLIN. E. MESTER, Paediat. danub. **2**:19 (July) 1947.

A case is described of a female child 2½ years of age in whom noma developed following pneumonia. Since the customary methods of treatment proved of no value, the following twofold treatment was devised. First, penicillin was administered to control the infection itself and, second, at the same time, vitamins, blood transfusions and a high protein diet were given to correct the deficiency states.

The condition became demarcated after a single course of 300,000 Oxford units of penicillin but became worse again when treatment was discontinued. These facts alone were considered a proof of the efficacy of penicillin in noma, but it was completely proved when, soon after a second course of 200,000 Oxford units, the spread stopped and recovery was complete.

FROM THE AUTHOR'S ABSTRACT.

Nervous Diseases

TREATMENT OF INFLUENZAL MENINGITIS. ABRAHAM LEVINSON, Illinois M. J. **94**:227 (Oct.) 1948.

A study was made of 60 patients with influenzal meningitis treated at the Children's Division of the Cook County Hospital, Chicago, from January 1942 to June 1948, with a comparison of the results of each type of treatment. The patients treated with sulfonamide compounds, penicillin and serum without streptomycin had a mortality rate of 48.5 per cent, and those treated with streptomycin had a general mortality rate of 9.8 per cent.

Of the 12 patients treated with streptomycin, sulfonamide drugs, penicillin and serum, 3 died. All 17 patients who were treated with streptomycin and sulfonamide compounds recovered. Two patients were treated with streptomycin only, and both recovered. Combining sulfonamide therapy and streptomycin is advised in order to inhibit secondary invaders.

In the last 22 patients all the streptomycin was given only intramuscularly, demonstrating that intrathecal therapy is not necessary. Levinson is of the opinion that 300,000 units of streptomycin every six hours is the proper dose. Use of streptomycin was continued until the patient stayed afebrile for three days. Intravenous administration of sulfadiazine was favored to begin with and then by mouth as soon as possible. The use of sulfadiazine was continued for five days after the administration of streptomycin was discontinued.

BARBOUR, Peoria, Ill.

NEUROPHYSIOLOGICAL CLUES TO AUDITORY ACUITY. LEO G. DOERFLER, J. Speech & Hearing Disorders **13**:227, 1948.

An attempt to utilize the galvanic skin responses as neurophysiologic clues to auditory acuity is described. The equipment recorded the Tarchanoff effect, or the actual electromotive force generated between two electrodes, presumably by the action of the sweat glands. The procedure necessarily varied from subject to

subject. Some subjects were instructed to respond by pressing a telegraph key when they heard a tone. It had been previously observed that such an action did not produce a galvanic skin response. Other subjects were told that they would hear tones of varying frequency and intensity but that they were to do nothing. In many subjects there appeared the complicating factor of adaptation. The subject gave a good response to the first few stimuli and then on repeated stimulation gave no reliable response. Subjects also varied tremendously in their response, some responding perfectly down to their thresholds of sensitivity as measured by audiograms, while other subjects often gave no consistent response, even at intensities well above threshold. Adaptation appeared to be overcome to a large extent through the use of an ascending rather than a descending intensity technic.

The second problem of subject variation was difficult, but a warning device, a small flashlight, helped in producing galvanic skin response. The most satisfactory results were obtained by telling the subject that the auditory stimulus would be presented sometime within a period of eight seconds after the light went out. All subjects in the experiment had substantially normal hearing, except 1 with a dip of 4,096 cycles. In the author's opinion, this research showed that emotionally charged speech material may result in a more reliable galvanic skin response, but the evidence is meager. The galvanic skin response offers a promising means of ascertaining auditory acuity.

PALMER, Wichita, Kan.

ELECTROENCEPHALOGRAPHY IN CHILDHOOD. JAMES G. HUGHES, New Orleans M. & S. J. **101**:268 (Dec.) 1948.

A lengthy and detailed discussion of the application of electroencephalography in childhood is presented. The technic used is described, and variations in the normal pattern in children at various age levels are noted. Its use in differentiating localized defects from generalized cortical defects, thus giving indications for possible surgical treatment, is pointed out. The presence of abnormal electroencephalograms in many children with serious behavior disturbances is significant.

MCGUIGAN, Evanston, Ill.

ACCIDENTAL INJURIES IN EPILEPTIC CHILDREN. MILTON R. AISENSON, Pediatrics **2**:85 (July) 1948.

The athletic privileges of convulsive children are often limited because of fear of injury. This hinders their development of motor skills and is an important cause of social maladjustment in childhood and later life. The records of 960 patients at a children's psychiatric hospital were reviewed. These children engaged in an identical athletic program, suitable to season and to the age of the child, under adult supervision. Among 750 nonconvulsive children, there were 18 fractures, 2 dislocations and 2 injuries to the eye, a total of 22 injuries and an incidence of 2.9 per cent. Among 210 convulsive children, there were 6 fractures and no other injuries, an incidence of 2.8 per cent. Since there is no extra risk of injury, convulsive children should be allowed to participate in physical education programs in camps and schools.

FROM THE AUTHOR'S SUMMARY.

THE RECOGNITION AND TREATMENT OF INCREASED INTRACRANIAL PRESSURE IN INFANCY AND CHILDHOOD. BARNES WOODHALL, Pediatrics **2**:533 (Nov.) 1948.

Recognition of increased intracranial pressure in infants and children is directly influenced by two anatomic factors: 1. The skull is an expansible structure, with open fontanels and infused suture lines. 2. The normal increment of brain volume

is trebled by 3 years of age and attains adult size only at 15 years. The roentgenogram of the skull of the growing child, therefore, differs from that of the adult and may reveal the imprint of the expanding hemisphere on its inner surface. Roentgenologic diagnosis must consider these variations in normal growth and is dependent on the demonstration of an abnormally large skull, convolutional atrophy, separation of suture lines and erosion of the sella turcica. Pressure of the normally growing brain on the skull is graphically demonstrated by roentgenogram in the clinical syndrome of craniosynostosis; pathologic alterations are best seen in advanced instances of brain tumor.

Study of roentgenograms of 100 consecutive patients with brain tumors showed that the presence of increased intracranial pressure could be suspected in 63. A major portion of the group presented a short and almost fulminating onset of symptoms, with about half complaining of symptoms of increased intracranial pressure (headache, vomiting and visual difficulty) and the remainder complaining of symptoms suggesting a specific neurologic defect (staggering gait and muscle weakness). In the neurologic examination of these 100 patients, 88 showed increased intracranial pressure through ophthalmoscopic examination alone. Other pathologic evidence included the presence of an enlarged head, a cracked-pot sound on percussion of the skull and cervical rigidity.

The prognosis for children of this age group with typical histories of tumors is favorable only in the group with cerebellar astrocytomas. The safety of surgical intervention in tumors in children of this age group has been greatly enhanced by technical advances; ignorance of the fundamental tumor process remains profound. The neurosurgeon is dependent on prompt and good pediatric diagnosis.

FROM THE AUTHOR'S SUMMARY.

USE OF MESOXALYL UREA (ALLOXAN) IN TREATMENT OF AN INFANT WITH CONVULSIONS DUE TO IDIOPATHIC HYPOGLYCEMIA. NATHAN B. TALBOT, JOHN D. CRAWFORD and C. CABELL BAILEY, Pediatrics **1**:337 (March) 1948.

The case history of an 8 month old infant with severe convulsions due to idiopathic hypoglycemia is described. Because of the poor prognosis and lack of other certain means of therapy, treatment of the hypoglycemia by means of mesoxalyl urea (alloxan) was undertaken with apparent success.

It is concluded that mesoxalyl urea (alloxan), though a potentially dangerous drug, may be worthy of further cautious trial in patients of the type described here.

FROM THE AUTHORS' SUMMARY.

TOXOPLASMIC ENCEPHALOMYELITIS. GABRIEL A. SCHWARZ, ELIZABETH KIRK ROSE and WILFRED E. FRY, Pediatrics **1**:478 (April) 1948.

Six cases of toxoplasmic encephalomyelitis in infants and children are presented. For all the patients the diagnosis was made on clinical grounds alone. All these patients are still living. A description of the pathologic findings in the retina of 1 is given. In an analysis of these 6 patients it was noted that the ocular findings were the most constantly occurring of all the features. Mental retardation was also noted in all 6. Cerebral calcifications were observed in all but 1 of the children.

The cases already reported in the literature are enumerated, and a review of the clinical features of toxoplasmic encephalomyelitis is given. The chief features noted in the infantile form are: (1) onset at birth or soon after, (2) convulsions, (3) bilateral communicating hydrocephalus, (4) bilateral focal chorioretinitis usually involving both maculas and (5) multiple calcifications in the brain.

It is the authors' opinion that this constellation of signs and symptoms should suggest the diagnosis of toxoplasmosis without recourse to the isolation of the protozoan or the securing of positive neutralization reactions.

FROM THE AUTHORS' SUMMARY.

ACUTE ATAXIA IN A TWENTY-MONTH-OLD FEMALE. MAURICE J. KELLER and SAMUEL KARELITZ, Pediatrics **1**:754 (June) 1948.

A case of ataxia of sudden onset in a 20 month old girl was observed over a period of six months. Encephalitis was thought to be the most likely diagnosis. She had bizarre manifestations, involving particularly the eyes, and unusual generalized startle reactions with varying visual and auditory stimuli. Similarities to the "electric chorea" of Dubini and Bergeron and to the myoclonic and the acute cerebellar forms of encephalitis were discussed. The only significant changes which appeared in the patient over the six month observation period were somewhat better coordination and the gradual development of explosive emotional reaction in response to the slightest lack of interest evidenced by the hospital personnel. Intelligence appeared unaffected by the disease.

FROM THE AUTHORS' SUMMARY.

THERAPY IN EPILEPSY. H. HOUSTON MERRITT, Wisconsin M. J. **47**:463 (May) 1948.

Cases of epilepsy may be subdivided into three groups. Classification into symptomatic and idiopathic epilepsy may be fallacious in respect to true underlying pathophysiologic causes. Classification according to the site of origin of the epileptic discharge is of especial value to the neurosurgeon. Classification according to clinical manifestations is of value for therapeutic considerations. The three types of clinical seizures are (1) petit mal, (2) grand mal (including jacksonian) and (3) psychic equivalent or psychomotor. Electroencephalographic changes are characteristic of each type.

Therapy must be divided into three categories: (1) elimination of factors of importance in the causation or precipitation of attacks, (2) improvement of general mental and physical hygiene and (3) use of medical therapy directed toward the elevation of the convulsive threshold. The choice of drug is governed by the type of seizure and by the response of the patient. Combinations of two or more drugs may be needed. Failure to obtain a good result is often due to inadequate dosage.

BAIRD, Wauwatosa, Wis.

SUBDURAL HEMATOMA IN INFANCY. T. STALTEN, Canad. M. A. J. **58**:63 (Jan.) 1948.

Stalten discusses the problem of subdural hematomas, after reviewing 28 cases. The frequency with which the diagnosis is missed is indicated by the fact that admission to the hospital in only 5 of the cases was with this diagnosis. The other diagnoses varied from hydrocephalus to nasopharyngitis, with convulsions, myatonia congenita, tetany and hypertonia. The diagnosis is established by the results of subdural tap. Trauma is considered to be the commonest etiologic factor and may be only slight. It is emphasized that the condition is much commoner than generally thought, and that it must be looked for to be found.

MCGUIGAN, Evanston, Ill.

MENINGITIS IN CHILDHOOD. N. SILVERTHORNE, Canad. M. A. J. **58**:255 (March) 1948.

Cases of meningitis over a twenty-five year period in the Hospital for Sick Children, Toronto, Canada, are reviewed, with presentation of data concerning incidence and mortality. Methods of treatment in past years are briefly reviewed and present methods outlined in detail.

McGUIGAN, Evanston, Ill.

ERB'S PALSY. B. WOLMAN, Arch. Dis. Childhood **23**:131 (June) 1948.

The end results of 37 cases of laceration of the peripheral nerve at birth (Erb's palsy) were investigated. The condition is slightly commoner in boys. Injury at birth to the supraclavicular portion of the brachial plexus is the accepted cause of the condition, and, therefore, skilled obstetric technic in delivery, particularly in the use of forceps, is the main factor in avoiding this paralysis.

Large babies are more likely to be injured. A large child in a primigravida needs special care with the delivery of the head and arms. Treatment must be carried out from birth. Children treated within the first month of life do uniformly well and results are 100 per cent successful. If treatment is delayed, contractures causing impaired function of the shoulder and elbow will develop quickly.

KELLY, Milwaukee.

H. INFLUENZAE MENINGITIS. I. A. B. CATHIE and S. D. v. WELLER, Arch. Dis. Childhood **23**:208 (Sept.) 1948.

A case of Hemophilus influenzae meningitis is presented in detail. Treatment with streptomycin was a total failure, and the disease was only partly controlled by use of penicillin and sulfonamide compounds. After three relapses, the disease was cured by the additional administration of H. influenzae rabbit antiserum.

KELLY, Milwaukee.

A CASE OF CEREBRAL ABSCESS. L. C. E. LINDON, Clin. Rep. Adelaide Children's Hosp. **1**:35 (May) 1947.

Lindon reports a case of frontal abscess following encephalitis, with apparent cure after aspiration and drainage followed by penicillin lavage. He states that this procedure is more logical than radical excision as practiced in America.

McGUIGAN, Evanston, Ill.

ENCEPHALOPATHY DUE TO LETHAL THALLIUM POISONING. E. MAYERHOFER and S. DIMITRIJEVIC, Paediat. danub. **1**:259 (May) 1947.

A child 2½ years of age was twice poisoned with thallium, on the second occasion lethally, through apparent criminal negligence. The symptoms corresponded to those commonly known, the clinical picture closely resembling the ophthalmoplegic form of Economo's lethargic encephalitis.

The first attack was somewhat similar to poisoning with lead or mercury. Mayerhofer and Dimitrijevic advance a new toxicologic theory and explain this phenomenon by the neighboring positions mercury, thallium and lead occupy in the periodic system of elements. This may also be the reason that in some instances poisoning from arsenic leads to symptoms similar to that from thallium.

FROM THE AUTHORS' ABSTRACT.

ACUTE CEREBRAL TREMOR AND ATAXIA IN YOUNG CHILDREN. A. DEKKER-JONKER, Nederl. tijdschr. v. geneesk. **92**:2912 (Sept. 18) 1948.

Between July 1947 and February 1948 in the suburbs of Haarlem, Netherlands, 8 children (6 boys and 2 girls) were observed with the morbid picture of an acute cerebral tremor. The ages of the children varied from 4 months to 3 years, but 1 child was 6 years of age. The symptoms arose sometimes after, sometimes simultaneously with, a febrile disease, among others, stomatitis, intestinal disturbance, bronchopneumonia and inflammation of the throat. The symptoms were a general or localized tremor, increasing on exertion, ataxia of the cerebral type and psychic changes: apathy or agitation. Sometimes the reflexes were increased. In 5 children examination of the cerebrospinal fluid showed no changes. The children were confined to their beds, and after some weeks or months they all recovered without sequelae (which have, however, been described in literature).

The causation of this morbid process is explained in different ways. In the first place, a toxic encephalopathy has been considered, but this possibility is contradicted by the fact that the symptoms usually arise after the acute illness and do not always increase when the original disease shows a relapse. In favor of the possibility of an independent virus infection is the simultaneous occurrence of a number of cases. In the third place, a relationship with the ataxic form of poliomyelitis has been considered, as at the time the first 4 patients with tremor were seen several cases of poliomyelitis occurred. However, the cerebrospinal fluid showed no abnormalities.

VAN CREVELD, Amsterdam, Netherlands.

Psychology and Psychiatry

WHY STAMMERERS SUFFER. SATYA NARAYAN PUROHIT, J. Speech Disorders **12**:419 (Dec.) 1947.

This article is on the problems of stuttering as seen by a stutterer. India has practically no source of corrective care for stutterers. Stutterers have difficulty with stuttering and suffer because of it only on account of the attitude of normal speakers. Stutterers have a terrific drain of energy due to the phobia associated with their being snubbed or sneered at or misunderstood in the past.

"In conclusion, a stammerer—until a specialist comes to his rescue and cures him—must neither be snubbed, nor thought abnormal, nor be sneered at and 'made a laughing-stock,' a target of typical indecent joking and mocking which will turn his life into a virtual hell through no fault of his own. He must be treated very sympathetically and be given a chance to lead a happy life on this crust of earth."

PALMER, Wichita, Kan.

A PROGRAM TO FOSTER ADJUSTMENT IN YOUNG CHILDREN. KATHERINE E. ROBERTS and C. ANDERSON ALDRICH, Pediatrics **3**:195 (Feb.) 1949.

As part of the long time program of service and research in the Rochester Child Health Institute, Rochester, Minn., each child as he reaches the age of 2½ years is invited to come in for an intelligence test. While the child is being tested, the mother talks with a psychologist and gives detailed information about the development and characteristics of the child. Habits of eating, sleeping and elimination are discussed, as well as management of the child at home, most effective methods used, his play and social life, his language and his emotional and personality development. The mother is invited to return for a conference with one of the psychologists, who interprets the results of the test and the interview and discusses

with her any questions she may have about her child. If it seems indicated, plans are made for further appointments with the appropriate specialist. In this paper some of the tentative findings of this survey are presented, and their implications for various specialists who work with children are discussed.

FROM THE AUTHORS' SUMMARY.

BENZEDRINE® AND DEXEDRINE® IN THE TREATMENT OF CHILDREN'S BEHAVIOR DISORDERS. CHARLES BRADLEY, Pediatrics **5**:24 (Jan.) 1950.

The effect of benzedrine® (*dl*-amphetamine) and dexedrine® (*d*-amphetamine) sulfates on the behavior of maladjusted children was studied in the somewhat controlled setting of a children's psychiatric hospital. Twelve years' experience with these drugs is reported, involving observations on 275 children who received benzedrine,® 113 who received dexedrine® and 82 who received both preparations. The most frequent optimal daily dose was 20 mg. of benzedrine and 10 mg. of dexedrine.® Specific behavior responses to the drugs approximated each other, both in quality and in frequency, with 50 to 60 per cent of the children becoming more subdued, 15 to 25 per cent showing no change, 20 per cent showing increased activity and 5 per cent showing an acceleration of progress in school only. Clinically, these reactions indicated 60 to 75 per cent with symptomatic improvement, 15 to 25 per cent with no change and 10 to 15 per cent with unfavorable responses. Children with a variety of clinical diagnoses were benefited, with no evidence of tolerance or addiction following prolonged administration.

Occasional undesirable physiologic side effects were noted with both preparations, most frequently during the first few days of treatment only. Approximately equal numbers of children responded more favorably to one drug than the other. In general, benzedrine® was noted to produce the more dramatic results, except with individual children in whom its side effects were more pronounced, in which patients use of dexedrine® proved more advantageous.

The conclusion is drawn that these drugs influence children's behavior by altering their emotional reactions to distressing situations. Both offer the practitioner readily available and easily controlled pharmacologic approaches to the symptomatic treatment of behavior disorders in children.

FROM THE AUTHOR'S SUMMARY.

BUT IS IT APHASIA? JEANETTE ANDERSON, Quart. J. Speech **33**:496 (Dec.) 1947.

Aphasia has become a kind of wastebasket designation for severe disturbances of speech that cannot be more accurately diagnosed. Of a group of 10 recently referred patients, only 2 were shown to have aphasic symptoms. The incidence of aphasic patients among speech-defective persons is about 0.3 per cent. Aphasias are manifested by disturbances of reception, retention or linguistic symbolism in the absence of inability to understand or produce written or spoken language because of general mental retardation, failure of the muscles of articulation, phonation or writing, defective hearing or any other physical condition acting to prevent any aspect of the speech act in association or symbolization. Two cases are presented to demonstrate this problem. Work in classification of aphasic manifestations is presented. Differential diagnostic measures are given with an illustrative case.

PALMER, Wichita, Kan.

ALLOWING YOUNG CHILDREN TO SET THEIR OWN PACE: BUILDING HUMAN EFFICIENCY. C. ANDERSON ALDRICH, Wisconsin M. J. **46**:225 (Feb.) 1947.

Much of modern child care acts to prevent the child from "doing his stuff." A liberalized and flexible routine, synchronized with the infant's own physiologic advances, makes for greater efficiency of the organism.

In the newborn period neglect of the significance of crying can produce a "problem child" at a very young age. In a child 6 months of age certain behavior may be considered "bad," as, for example, fear of strangers, when it really is only an aspect of increased efficiency—in the example cited, of increasing visual competence. When the child is in the toddler stage, penning him up or insisting on rigid habits of eating, sleeping or elimination may prevent the development of the child's neuromuscular mechanisms.

The physician who is proficient in the art of the practice of medicine synchronizes his instructions to the parents with the natural rhythm of growth in his little patients.

BAIRD, Wauwatosa, Wis.

Diseases of the Genitourinary Tract

DYSGERMINOMA OF THE OVARY IN A FOUR-YEAR-OLD GIRL WITH METASTASES CLINICALLY SIMULATING WILMS' TUMOR AND ADRENAL NEUROBLASTOMA. F. B. MANDEVILLE, P. F. SAHYOUN and L. E. SUTTON JR., J. Pediat. **34**:70 (Jan.) 1949.

The authors report on a 4 year old Negro girl with bilateral dysgerminoma. She died after rupture of the left ovary with resultant hemoperitoneum. Widespread metastases were seen at autopsy.

MACDONALD, Pittsburgh.

MAJOR PELVIC PATHOLOGY IN CHILDREN. DANIEL W. GOLDMAN and PARKER K. HUGHES, J. Pediat. **35**:77 (July) 1949.

Indefinite abdominal pains in female children may be associated with disorders of the pelvic organs. In addition to the routine abdominal examination, the pediatrician should perform a rectal examination on such children. In some instances vaginal examination may be necessary.

MACDONALD, Pittsburgh.

URETEROCELE IN INFANCY AND CHILDHOOD. ROBERT E. GROSS and H. WILLIAM CLATWORTHY JR., Pediatrics **5**:68 (Jan.) 1950.

Ureteroceles are abnormalities which result from congenital stenosis of a ureterovesical junction. That portion of the ureter which obliquely traverses the bladder wall becomes ballooned out so that it projects into the lumen of the bladder. This bulging mass in the bladder may be 1 cm. or more in diameter. The lesions are commoner in females. The outstanding symptoms are referable to pyuria, which appears in most cases. There may be abdominal pain or pain in the flank from the ureteral obstruction. In some patients the ureterocele may lodge in the outlet of the bladder and block the urinary flow from the entire urinary tract, in this way giving rise to damage in both kidneys. In rare instances a ureterocele may prolapse through the urethra of the female patient. Ureteroceles are apt to give rise to symptoms in infancy or childhood, but in some cases they are not manifest until later years. Intravenous pyelography and cystography will often give conclusive evidence of the presence of the abnormality, but in some patients cystoscopy will be necessary to establish the diagnosis.

Ureteroceles are not difficult to treat. They should never be excised, because such surgical attack is apt to destroy the ureterovesical valve and permit reflux of urine from the bladder to the upper part of the urinary tract, a complication which results in increasing hydronephrosis and pyelonephritis. A ureterocele mass will collapse from mere longitudinal incision of its dome for a distance of 5 to 10 mm. This effectively relieves the ureteral obstruction and is the most important step in the treatment of any existing urinary infection. Chemotherapy is a valuable adjunct in the treatment of pyuria, but it will have permanent benefit only if the mechanical obstruction has been completely eradicated. In babies and small children, it is preferable to avoid incision of a ureterocele by cystoscopic instrumentation; it is safer to open the bladder and incise the structure under direct vision. The results of the latter type of therapy are extremely gratifying, and in most instances such conservative measures will permit saving of the kidney on the affected side.

FROM THE AUTHORS' SUMMARY.

TORSIO TESTIS. K. KUCEROVÁ-MEISLOVÁ, Pediat. listy **2**:255, 1947.

Four cases of torsio testis are described. Details are given of the clinical picture, the pathogenesis and therapy of the disease.

FROM THE AUTHOR'S SUMMARY.

PERINEPHRITIS AND PERIRENAL ABSCESS IN CHILDHOOD. AUGUSTO GENTILI, Policlinico inf. **15**:419 (Sept.) 1947.

The author, after seeing 3 cases of perinephritic abscess, which came under his observation with a wrong diagnosis, notes the etiologic, pathogenetic, anatomicopathologic and clinical significance of perinephritis and of perinephritic abscess in childhood.

He states the place that this disease occupies in the pathologic lesions of children and outlines the difficulties that are but rarely overcome to reach the right diagnosis.

FROM THE AUTHOR'S SUMMARY.

TREATMENT OF CRYPTORCHISM. ALFREDO RODRIGUEZ CASTRO, Arch. de pediat. d. Uruguay **11**:583 (Nov.) 1947.

The author points out that it is not uncommon to find children in whom the testes do not descend in the normal period of time. He is of the opinion that in many of these descent will occur before puberty without any treatment. He states that, except in rare cases, one should wait until the age of 10 years before attempting to correct cryptorchism. The best prognosis, in his opinion, may be given when endocrine therapy and surgical treatment are combined.

KALISKI, San Antonio, Texas.

RENAL RICKETS. OSCAR B. CORREA and HILDA CORTES DE COOPER, Rev. chilena de pediat. **7**:172 (March) 1947.

The authors describe a case which, in their opinion, fulfils the criteria for renal rickets. The patient, a boy 14 years of age had pronounced renal insufficiency, with acidosis and nitrogen retention, together with skeletal deformities and roentgenologic findings of active rickets. Because of a history of polydipsia and polyuria at 2 years of age, they discuss the possibility of early renal damage. They also mention the possible role of a disturbance of the diencephalopituitary system. The patient exhibited a lowered glucose tolerance, which the authors postulate

might have been due to the combined effects of renal failure, anemia and acidosis. They mention, as a rare possibility, a disturbance of the pituitary as being responsible for these phenomena.

KALISKI, San Antonio, Texas.

SYNECHIA OF THE VULVA IN CHILDREN. KAREL VESELÝ, Ann. pædiat. **170**:151 (March) 1948.

The author recommends operation on vulval synechia with thermocautery. He prefers this method to blunt separation. In the gynecologic outpatient department of a university hospital, in Prague, Czechoslovakia, vulval synechia was seen in 1.3 per cent of 1,400 children.

FROM THE AUTHOR'S SUMMARY.

RUDIMENTARY OVARIES (OVARIAN AGENESIS) IN GIRLS. A. J. M. HOLMER, Nederl. tijdschr. v. geneesk. **92**:1130 (April 17) 1948.

The syndrome of Turner consists of retarded growth, sexual underdevelopment, pterygium colli (webbed neck) and cubitus valgus. With this syndrome other congenital defects may be associated, such as bilateral ptosis, bilateral cataract, limitation of the visual fields, absence of pigment in the retina, spinal bifida, deafness, mental retardation and coarctation of the aorta. This syndrome is due to impaired development of the ovaries, and, as a result, the urine contains small amounts of the 17-ketosteroids, while the excretion of gonadotropin is increased. The dwarfism is not one of the characteristic symptoms but is dependent on the time ovarian development ceases. Castration of girls in early childhood does not inhibit growth, as a rule. In these cases the limbs are long in proportion to the body length and the estrogens stimulate the ossification of the epiphysial plates. The pituitary dwarf differs, however, from the ovarian dwarf. The first is below average height and thin, the ossification of the epiphysial plates is retarded and the urine contains but small amounts of gonadotropin and of 17-ketosteroids.

The present series consisted of 9 girls and of these only 1 was not below the normal average height (the height was 165 cm.); she had a basal metabolic rate of —4 per cent and the cholesterol content of the serum was 325 mg. per hundred cubic centimeters. The other girls' height varied from 132.5 cm. to 150 cm. and the basal metabolic rate between +4 and +39 per cent.

One of the remaining 8 children is described also. Her height was only 145.5 cm. and her arm span 157 cm. Infantile face, webbed neck, broad chest, cubitus valgus, absence of axillary hair, underdevelopment of the pubic hair and of the breasts, poorly developed external genitals and nonpalpable uterus and ovaries were the other signs. The sella turcica was normal. Ossification of the epiphysial plates was not entirely complete. However, osteoporosis was not observed. The palate was high and narrow. The blood pressure was 115 systolic and 75 diastolic. The mental development was normal. The urine contained a large amount of gonadotropin and little 17-ketosteroid.

The treatment is symptomatic and consists of daily administration of large doses of alpha-estradiol (dimenformon®), 50,000 to 100,000 units. Implantation of ovarian tissue in the abdomen should make pregnancy possible if the fallopian tubes and uterus are present. The development of the breasts is due not only to the estrogens but also to stimulation by a pituitary hormone.

VAN CREVELD, Amsterdam, Netherlands

Diseases of the Ductless Glands: Endocrinology

THE ACTION OF HUMAN PROSTATE SLICES ON α-ESTRADIOL AND ESTRONE. ALBERT L. LEHNINGER and WILLIAM WALLACE SCOTT, Endocrinology **40**:9 (Jan.) 1947.

Human prostate slices remove large amounts of estrone or α-estradiol from a buffered suspending medium containing these hormones on incubation at 38 C. Estrone removed from the medium is apparently adsorbed, since it can be recovered by extraction of the slices with ethyl alcohol and ether. The same effect is given by heat-inactivated prostate or rat liver slices, indicating that the adsorption is not a metabolic process.

JACOBSEN, Buffalo.

MOBILIZATION OF ALKALINE PHOSPHATASE IN THE UTERUS OF THE MOUSE BY ESTROGEN. WILLIAM B. ATKINSON and HERBERT ELFTMAN, Endocrinology **40**:30 (Jan.) 1947.

Injection of estrogen into the ovariectomized mouse is followed by a pronounced increase of alkaline phosphatase in the uterine glands and luminal epithelium and in the circular layer of the myometrium. On the basis of these observations and previous data on the effect of estrogen on uterine metabolism, it is suggested that the mobilization of alkaline phosphatase by estrogen is a link in the mechanism by means of which estrogen affects lipid and carbohydrate metabolism in the uterus.

JACOBSEN, Buffalo.

THE METABOLIC SIGNIFICANCE OF PROTEIN-BOUND IODINE OF PLASMA: A STUDY OF ITS CONCENTRATION UNDER VARIOUS CONDITIONS AND OF ITS RATE OF FORMATION AS MEASURED WITH RADIOACTIVE IODINE. I. L. CHAIKOFF, ALVIN TAUROG and W. O. REINHARDT, Endocrinology **40**:47 (Jan.) 1947.

The fraction of plasma iodine designated "protein bound" is the iodine that is precipitated from plasma along with its proteins by such agents as tungstic acid, zinc hydroxide or acetic acid in the presence of heat and, in addition, cannot be freed from these proteins by simple washing. Although the chemical identity of this fraction is as yet poorly understood, its concentration in plasma has gained wide use as an indicator of thyroid activity in man.

In the present investigation, an attempt has been made to determine the metabolic significance of plasma protein-bound iodine. Its concentration in plasma was studied in rats shown to be completely deprived of thyroid tissue and in rats and guinea pigs in which hyperthyroidism had been induced. The use of radioactive iodine as a labeling agent also made possible a study of the rate of formation of protein-bound iodine in both states of thyroid activity.

As a result of the experiments, it is suggested that the rate of conversion of injected radioactive inorganic iodine into protein-bound iodine of plasma is a useful guide to thyroid activity.

JACOBSEN, Buffalo.

THE EFFECT OF HYPERGLYCEMIA ON INSULIN SECRETION AS DETERMINED WITH THE ISOLATED RAT PANCREAS IN A PERFUSION APPARATUS. EVELYN ANDERSON and JOSEPH A. LONG, Endocrinology **40**:92 (Feb.) 1947.

The technic for removal of the pancreas and its maintenance in a perfusion apparatus is described.

When the pancreas is perfused with blood which has a low glucose content, insulin is not secreted in an amount detectable by the assay method used.

A high glucose level in the perfusate stimulates the islet cells directly to secrete insulin.

It is concluded from these observations that the method described for the perfusion of the pancreas is sufficiently sound within certain physiologic limits to be used for testing the hormonal influences on insulin secretion.

JACOBSEN, Buffalo.

SUPPRESSION OF INSULIN SECRETION BY THE GROWTH HORMONE OF THE ANTERIOR PITUITARY AS DETERMINED WITH THE ISOLATED RAT PANCREAS IN A PERFUSION APPARATUS. EVELYN ANDERSON and JOSEPH A. LONG, Endocrinology **40**:98 (Feb.) 1947.

The diabetes which is produced by the administration of extract of the anterior lobe of the pituitary is the result of an interplay of several factors. These include the direct effect of anterior pituitary extract on (1) the pancreas, (2) other endocrine glands, especially the adrenal glands and the thyroid, and (3) other tissues, such as muscle and liver. The interaction of these various factors and their impact on the entire organism make the problem of pituitary diabetes exceedingly complex. An understanding of the separate factors is necessary before the problem as a whole can be analyzed. This paper deals with an attempt to study an isolated factor, namely the direct effect of anterior pituitary extract on the insulin-producing cells of the pancreas.

The experimental data reported here do not support the concept of a pancreatropic hormone of the pituitary, but rather the reverse, namely, that the anterior lobe of the pituitary contains a factor which inhibits insulin secretion. The observation that inhibition is obtained with a purified preparation of growth hormone and is not obtained with either adrenal cortical hormone or thyroxin suggests that it is the growth hormone rather than the adrenocorticotrophic or thyrotrophic hormone which acts directly on the islet cells. This does not exclude the adrenocorticotrophic and thyrotrophic hormones as diabetogenic factors acting in some manner on extrapancreatic tissues.

JACOBSEN, Buffalo.

CUSHING'S SYNDROME IN CHILDREN. A. L. CHUTE, G. C. ROBINSON and W. L. DONOHUE, J. Pediat. **34**:20 (Jan.) 1949.

Chute and his colleagues report a case of Cushing's syndrome in an 8 year old girl. She died two days after the removal of one adrenal gland. Autopsy showed hyaline changes in pituitary basophils, bilateral nodular hyperplasia of adrenal cortex, fatty liver and osteoporosis. This is the thirty-third case of Cushing's syndrome in the literature and the eighteenth that has come to autopsy. The authors discuss the theoretic evidence that the disease is adrenal in origin. They point out, however, that hyalinization of basophils in the pituitary is the most constant pathologic change in the disease.

MACDONALD, Pittsburgh.

LIVER DAMAGE BY DESOXYCORTICOSTERONE. E. S. SINAIKO and H. NECHELES, Science **109**:37 (Jan. 14) 1949.

When normal dogs were administered desoxycorticosterone acetate, 5 mg. daily for five days, followed by a single dose of 25 mg. after a week, and given 1 per cent salt solution to drink, pathologic changes in the liver occurred regularly. These consisted of hyperemia, central focal necrosis, cloudy swelling, fatty degeneration and pigmentation of the Kupffer cells. Changes in other organs were inconstant. Control animals given 1 per cent salt solution to drink showed only occasional cloudy swelling.

FORBES, St. Louis.

WATERHOUSE-FRIDERICHSEN SYNDROME. I. SACKS, South African M. J. **23**:426 (May 28) 1949.

Two patients with epidemic meningococcic cerebrospinal meningitis (Waterhouse-Friderichsen syndrome), one of whom lived, are reported on. The patient who recovered was treated with massive doses of penicillin, sulfathiazole, sulfadizine, nikethamide and adrenal cortex extract. No doses are given other than for penicillin.

McGUIGAN, Evanston, Ill.

PROTAMINE ZINC-INSULIN IN THE TREATMENT OF INFANTILE DIABETES. JULIEN MARIE, P. SERINGE and M. GUÉNIOT, Arch. franç. de pédiat. **3**:497, 1946.

An extensive monograph is presented, outlining with careful attention every detail of the management of diabetes in infants through the use of protamine zinc-insulin injection. The method is contrasted with others and significant case reports are appended, with an extensive bibliography.

AMESSE, Denver.

Diseases of the Muscles, Bones, Joints and Lymph Nodes

HIP LESIONS OF INFANTS AND CHILDREN SEEN AT THE NEWINGTON HOME AND HOSPITAL FOR CRIPPLED CHILDREN. GILBERT W. HEUBLEIN, LOUIS BERNSTEIN and B. J. HUBENET, Radiology **51**:611 (Nov.) 1948.

A wide variety of congenital and acquired diseases and deformities of the hip is discussed and illustrated with roentgenograms. Rare lesions of myositis ossificans, achondroplasia and fragilitas ossium are shown. This article should be of special interest to the young physician just starting his residency in pediatrics, orthopedics or roentgenology.

ANSPACH, Chicago, Ill.

EFFECTS OF CONTINUOUS RADIATION ON CHICK EMBRYOS AND DEVELOPING CHICKS: I. GROWTH RATE, GONADS, AND BONE. SHIELDS WARREN and FRANK J. DIXON, Radiology **52**:714 (May) 1949.

The age of the ova was an important factor in determining response to radiation. All injections of isotope P^{32} during the first eight days of incubation destroyed the ova. All injections after the fourteenth day of incubation, in spite of increased radiation, failed to destroy all ova. A week or so after radiation to the ova, the remainder of the ovary was hyperplastic but histologically showed no evidence of injury. Female chicks failed to show secondary sex characteristics that were demonstrated in the male. The effects of P^{32} injected into the yolks early was more concentrated on bone after the ninth day of incubation. The concentration of P^{32} was directly proportional to the degree of calcification. The cartilage cells of the epiphysis were more radiosensitive than the osteoblasts and osteoclasts. Grossly, the bones were smaller and lighter than normal but symmetrically formed. Over-all growth retardation resulted in dwarfism. The testes and ovaries were the most radiosensitive organs and the least able to recover from injury. Ova became more radioresistant as they matured.

ANSPACH, Chicago.

LIPODYSTROPHY. M. E. MACGREGOR, Proc. Roy. Soc. Med. **40**:533 (July) 1947.

Lipodystrophy is reported in an infant 8 months of age. From birth his limbs, especially his legs, were thin; their strength was apparently normal, and their movements were free. On examination, the limbs were observed to be muscular,

with but little subcutaneous fat on the legs and some deficiency of fat in the forearms. The face and trunk were normal. The roentgenograms of limb bones and the electrical reactions of muscles of the arms and legs were normal. No treatment was prescribed.

WILLIAMSON, New Orleans.

LEONTIASIS OSSEA. EMLYN LEWIS, Proc. Roy. Soc. Med. **41**:864 (Dec.) 1948.

This case of leontiasis ossea was reported in a boy, aged 11 years. He was referred to the hospital as having a sarcoma of the right maxilla with nasal obstruction on the right.

WILLIAMSON, New Orleans.

OSTEOPETROSIS (MARBLE BONES). EMLYN LEWIS, Proc. Roy. Soc. Med. **41**:864 (Dec.) 1948.

The patient, a boy of 9 years, was referred to the hospital because of osteomyelitis of the lower jaw which started in February 1947. Roentgenologic examination for osteomyelitis of the jaw showed typical marble bone appearance, together with extensive osteomyelitis of the right side of the mandible. The report of the results of blood examination and of the operation accompanies the case report.

WILLIAMSON, New Orleans.

PENCILLIN IN CHRONIC DEFORMING RHEUMATISM OF SEPTIC ORIGIN. J. M. MACERA and J. C. OYHENART, Arch. argent. de pediat. **27**:97 (March) 1947.

This is a case report. The classification of septic rheumatism by Costa Bertani is given. It is considered that the case reported belongs to the second group, that is, a severe, febrile, acute polyarticular form.

ROJAS, Boston.

VERTEBRA PLANA OSTEONECROTICA. MARC NEYROUD, Ann. paediat. **168**:19 (May) 1947.

The author describes a case of vertebra plana osteonecrotica (Calvé) which occurred in a boy 4½ years of age without apparent cause, and which was discovered roentgenologically three weeks after the first clinical signs became manifest. The author discusses the differential diagnosis. This is evidently the illness which Calvé described in 1924 as osteochondritis vertebralis infantilis. In reality its origin is not inflammatory but osteonecrotic. The condition should be included among the aseptic bone necroses and is, therefore, far better named vertebra plana osteonecrotica. Treatment is extension and administration of citric acid.

FROM THE AUTHOR'S SUMMARY.

Diseases of the Eye

ANGIOSARCOMA OF THE ORBIT. P. V. CARELLI and J. P. CANGELOSI, Am. J. Ophth. **31**:453 (April 1) 1948.

Carelli and Cangelosi report a case of angiosarcoma of the orbit in an 11 year old girl. The tumor was removed, and there was no metastasis at the end of thirty months.

REESE [ARCH. OPHTH.].

RETROLENTAL FIBROPLASIA AND LIGHT. W. R. HEPNER, ARLINGTON C. KRAUSE and M. EDWARD DAVIS, Pediatrics **3**:824 (June) 1949.

To discover whether exposure of the eye to light played any role in the development of retrolental fibroplasia, the authors covered the eyes of 5 premature infants,

with weights at birth ranging from 1,075 to 1,350 Gm. from shortly after birth until a weight of 2,000 Gm. was reached (thirty-five to sixty days). All received vitamin K, 15,000 units of vitamin A as vi-penta* daily, blood transfusions to prevent severe anemia and modified cow's milk formulas. They were kept in incubators supplied with oxygen for the first weeks of life.

Four showed retrolental fibroplasia and 1 did not. At the time of discharge from the nursery for premature infants, no defect was found in the eyes of the 4 infants who later had retrolental fibroplasia. Successive examinations of the 4 affected infants revealed progressive ocular abnormalities. Retrolental fibroplasia is apparently a process which advances and which may not be a true congenital defect. It may be a congenital developmental defect, but even this is still not proved. It is concluded that exposure of the eye to light is not an etiologic factor of retrolental fibroplasia in premature infants.

FROM THE AUTHORS' SUMMARY.

THE MANAGEMENT OF CONCOMITANT CONVERGENT STRABISMUS. FRANK D. COSTENBADER, South. M. J. **42**:617 (July) 1949.

While this article was written primarily for ophthalmologists, it bears reading by pediatricians. It is a discussion of the physiologic aspects, clinical classification and treatment of concomitant convergent strabismus. The objectives of treatment in this group of esotropia are: (1) to regain and maintain vision in each eye from early childhood, (2) to regain binocular alinement as early in infancy and childhood as possible and to maintain it and (3) to correct insecure vision, poor amplitudes or poor binocular habits. All these conditions have their onset in children under the age of 6 years, and must be recognized and treated as soon as possible after onset.

LOGAN, Rochester, Minn.

CONGENITAL BLINDNESS ANOMALY. W. M. G. WILSON, Canad. M. A. J. **60**:580 (June) 1949.

The pedigree of an Indian family is shown, in which several boys over a period of six generations were born blind. A gene causing developmental ocular arrest appears to be present as a sex-linked characteristic.

McGUIGAN, Evanston, Ill.

BILATERAL MICROPHTHALMIA—REPORT OF A CASE. J. A. KEEN, South African M. J. **23**:518-520 (June 25) 1949.

A case of bilateral microphthalmia is presented. The entire visual apparatus was involved. The optic tracts were only thin strands; the lateral geniculate bodies were practically absent, and no visual stria could be found in the cortex.

McGUIGAN, Evanston, Ill.

Skin Diseases; Allergy

SENSITIVITY FROM INSUFFLATION OF THE POWDERED SULFONAMIDE COMPOUNDS IN ACUTE INFECTIONS OF THE NOSE AND THROAT. HOWARD C. BALLENGER, Arch. Otolaryng. **46**:52 (July) 1947.

Sulfonamide powders insufflated into the nose and sinuses cause fewer incidents of the symptoms of sensitivity (less than 0.5 per cent) than sulfonamide drugs

taken by mouth (1.4 per cent) and sulfathiazole cream applied topically as minor surgical treatment (5.5 per cent).

KIMBALL, Evanston, Ill.

BLOOD PROTEIN DEPLETION IN INFANTILE ECZEMA. LEON Z. WOLPE, California Med. **67**:156 (Sept.) 1947.

Hypoproteinemia has been demonstrated in a large percentage of cases of infantile eczema and is a hazard in elimination diets. Knowledge of protein deficits will aid in preventing death from "nutritional crises."

Intravenous administration of amino acids is recommended for treatment of protein deficiency.

PRYOR, Redwood City, Calif.

LYSIS IN VITRO OF SENSITIZED LEUCOCYTES BY RAGWEED ANTIGEN. THEODORE L. SQUIER and HOWARD J. LEE, J. Allergy **18**:156 (May) 1947.

Lysis in vitro of sensitized leukocytes, evidenced by a reduction of approximately 43 per cent in the total number of cells, resulted from the addition of short ragweed antigen to heparinized whole blood from patients sensitive clinically and by cutaneous tests to ragweed pollen. The polymorphonuclear cells were chiefly affected.

Leukocyte disintegration was inhibited by heating other portions of the same samples of blood for one hour at 56 C. to inactivate the ragweed-sensitizing antibody (reagin). No significant change in the total number of leukocytes occurred after the addition of ragweed antigen to such inactivated bloods.

No significant reduction in the total number of leukocytes occurred after the addition of ragweed antigen in the manner described to unheated samples of blood from ragweed-sensitive patients treated adequately by injections of ragweed antigen.

FROM THE AUTHORS' SUMMARY.

SOME PROBLEMS OF ATOPIC DERMATITIS IN INFANCY AND CHILDHOOD. LOUIS WEBB HILL, J. Allergy **18**:181 (May) 1947.

This article was one of a group presented at a symposium on eczema-dermatitis at the annual meeting of the American Academy of Allergy.

The author is of the opinion that eczema-dermatitis in infancy and childhood is a complicated problem and that at present treatment is not satisfactory. The practical therapy in the atopic form of dermatitis consists in removing from the diet and environment those allergens to which the child is sensitive and in treating the skin locally with all the dermatologic skill that one has.

HOYER, Cincinnati.

THE SENSITIZING FACTOR IN MERTHIOLATE [SODIUM ETHYLMERCURITHIOSALICYLATE]. FRANCS A. ELLIS, J. Allergy **18**:212 (May) 1947.

In persons sensitive to sodium ethylmercurithiosalicylate (merthiolate®) the thiosalicylic acid radical is the usual sensitizing factor. Approximately 50 per cent of persons tested were sensitive also to the mercury radical.

HOYER, Cincinnati.

Society Transactions

AMERICAN PEDIATRIC SOCIETY

Grover F. Powers, M.D., President
IN JOINT SESSION WITH

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

S. Graham Ross, M.D., President
Fifty-Eighth Annual Meeting, Quebec, Canada, May 24 to 26, 1948

Humanizing Hospital Experiences: Presidential Address. Dr. Grover F. Powers, New Haven, Conn.

This paper was published in full in the October 1948 issue of the American Journal of Diseases of Children, page 365.

Symposium on Preventive Mental Hygienic and Psychotherapeutic Aspects of Pediatric Practice

Psychotherapeutic Role of the Pediatrician. Dr. Milton J. E. Senn, New York.

Psychiatry, pediatrics, psychology and education have made contributions to the field of psychotherapy. This paper attempts to evaluate the essential ingredients for successful therapy which are common to each of these disciplines. The conclusion is reached that the constituent principle in the therapeutic process lies in the interpersonal relationships.

Orientation or Training in Child Psychiatry for the Pediatrician at the James Jackson Putnam Children's Center. Dr. Marion C. Putnam, Roxbury, Mass.

The James Jackson Putnam Children's Center is a child guidance clinic for the study and treatment of emotionally disturbed preschool children and their parents. It differs from the usual child guidance clinic in that it adds a nursery school to the familiar services of psychiatrists, psychologists and social workers. All these services are closely integrated for the pursuance of treatment, research and teaching.

One way vision screens in the nursery school enable the pediatrician or psychiatrist in training to observe a far wider range of children than he himself can possibly take in treatment. Of particular importance to the pediatrician is the fact that the age range of the children, from about 18 months to 5 years, familiarizes him with emotional development during the important formative years. The fundamental significance of the parent-child relationship is brought home to him not only through staff discussions but also through direct observation, since mothers must often remain in the nursery for many weeks because of their own anxiety and that of their children.

The addition of a well baby conference with ample opportunity for leisurely interviews with the mothers and direct observation of the developing infant under psychiatric supervision helps to round out the pediatrician's experience and training.

Psychotherapeutic Aspects of Pediatric Practice. Dr. Hilde Bruch and Dr. D. J. McCune, New York.

The purpose of this paper is to draw attention to the psychotherapeutic possibilities inherent in the practice of pediatrics. There has been increasing awareness of the need for more attention to the emotional problems of childhood. This recognition has been accompanied with a certain uneasiness about the dangers and difficulties which the management of psychologic problems would involve. Such objections might be justified if one considers as an approach to psychologic problems only the special psychotherapeutic technics which have been evolved for the treatment of neuroses and psychoses.

The physician-patient relationship (which in pediatric practice is frequently a physician-mother of patient relationship) carries within itself psychotherapeutic possibilities fundamentally the same as those which operate in the most intricate psychotherapeutic situation. Application of modern psychiatric knowledge to pediatric practice has usually been in the direction of outlining specific methods of child rearing, such as the advocation of self-demand feeding as opposed to scheduled feeding. The possibilities of an individualized utilization of the interpersonal situation has been by and large overlooked. This aspect is illustrated by case histories showing the danger of indiscriminate use of "modern" psychologic methods in the care of infants and children and the need for a more individualized approach. Other examples include the psychologic problems of the medical management of chronically sick and handicapped children.

A Program to Foster Adjustment in Young Children. Dr. Katherine E. Roberts and Dr. C. Anderson Aldrich,† Rochester, Minn.

As part of the long range program of service and research in the Rochester Child Health Institute, each child as he reaches the age of 2½ years is invited to come in for an intelligence test. While the child is being tested, the mother talks with a psychologist and gives detailed information about the development and characteristics of the child. Habits of eating, sleeping and elimination are discussed, as well as the management of the child at home, the most effective methods used, the play and social life of the child and his language, emotional and personality development.

The mother is invited to return for a conference with one of the psychologists, who interprets the results of the test and the interview and discusses with her any questions that she may have about her child. If it seems indicated, plans are made for further appointments with the appropriate specialist.

In this paper some of the tentative findings of this survey are presented and the implications for various specialists who work with children are discussed.

DISCUSSION

Dr. A. Ashley Weech, Cincinnati: So many aspects of the problems of preventive mental hygiene have been touched on in the papers presented by Dr. Senn, Dr. Bruch, Dr. Putnam and Dr. Roberts that it cannot be out of place to bring up still another topic which so far has not been discussed. The topic is appropriately introduced by quoting an aphorism of the immortal Joseph Brennemann, "Even death loses some of its sting when ushered in by a specialist." Since attaining the doubtful distinction of being a professor, it has fallen to my lot many times to be called to usher in death. While muttering wonderingly the Brennemann aphorism, I have also reflected that in all my time as a medical student and house officer there was never any instruction in how to behave before, in what to do for, in what

† Deceased.

to say to distraught parents when the death of a child was impending. Kindness, sympathy, understanding, willingness to listen to trivial talk are important parts of what is needed. There is, however, another part which, if specifically inquired for, can often be used to bring courage and acceptance in the hour of distraction. At times like these in nearly every family one or the other of the parents is undergoing augmented suffering through feelings of personal guilt. Questions which they fear to have answered formulate in their minds: "Am I to blame for this illness because I let her do this or that?" "Is this illness the punishment sent by an Almighty Deity for some act or neglect of mine?" Comfort and courage are gained when such unfounded fears are brought into the open and reasoned away.

When I left Cincinnati to come to this meeting, there was in one of the wards a little boy awaiting operation for a glioma of the brain stem. The outlook was, of course, bad and the parents were overcome with grief. After some conversation in private, the father confessed to a major source of concern. There were two children in the family, the patient and an older sister. They lived in the home of a childless and widowed sister of the father. The father had devoted many hours each week to his daughter but care of the little boy had been usurped almost entirely by the aunt. For some time prior to the onset of illness the aunt had been accusing her brother of neglecting his son and spending too much time with his daughter. It is not difficult to understand the aunt's reactions. Childless herself, the nephew in her home provided a natural outlet for strong maternal yearnings and she gave way so fully to the yearnings as to create a need for self justification. The attempt to justify took the form of accusing her brother of neglect. But the father did not understand. The development of a tragic illness had created a lurking fear that he was being punished for the neglect. He was desperately in need of understanding and reassurance. These I was able to give.

Several months ago in another family a child died in the operating room during a lobectomy. One of the staff physicians broke the news to the family and asked for permission for a postmortem examination. For a long while permission was categorically refused on the illogical ground that the child had already suffered enough. The physician then discovered that the parents' reaction to death was enmeshed with feelings of personal guilt. They believed it to be their fault that they had not recognized sooner the gravity of the illness and sought the advice of a specialist. The physician patiently encouraged the parents to tell again the whole story of the illness, a story of first one physician and then another who, through no fault of the parents, had failed to make the diagnosis. When the story was over, the physician commented simply that he was deeply moved by the obvious care and devotion that had been lavished on the child, that rarely had he encountered parents who had discharged more faithfully the responsibilities of parenthood. Then, he explained again the reasons autopsies are done and asked for signatures on the permit. The paper was signed at once and, while doing so, the mother commented that she knew now she was doing the right thing and that she would always feel better because she had signed the paper.

In another family a small daughter was dying of leukemia. There was no reason to question the diagnosis, and the quality of symptomatic care was as good as could have been wanted. Only the mother's mother, the child's grandmother, could not accept what she was told. She insisted that the child be moved to a hospital in another city in quest of another opinion. The whole family was torn with worry and indecision because financially they could not afford the trip. A medical friend of mine who told me this story was finally consulted. In a long talk with the grandmother, he found the true reason for her perturbation. One of the

physicians had tried to explain the nature of leukemia and in doing so stated that it is "something like cancer." The physician did not know that the grandmother's mother and brother had died with cancer. The grandmother was sure that her granddaughter's illness could be traced to "bad blood" inherited from her, hence her desperation. My friend took the time to convince her that the fears were groundless. She was then at peace and satisfied with what was being done.

Dr. Allan M. Butler, Boston: Often when psychiatrists appear before physicians, they suffer from certain inferiority complexes manifest in their trying to "sell" psychiatry. I hope this society can assure its child psychiatrists that they need not make any effort to "sell" child psychiatry to us. In listening to this discussion I found it was difficult to make up my mind whether child psychiatry, and all psychiatry perhaps, is in its infancy, or whether it knows so much that all it has to do is to teach pediatricians what child psychiatrists know. Yet I am sure child psychiatrists accept the fact that their branch of medical knowledge is in its infancy. As well as the necessity for pediatricians to learn what child psychiatrists already know, psychiatrists should stress their own endeavors to acquire knowledge. Those of us who are interested in the development of child psychiatry should think of it much as we do of any other research effort to acquire knowledge. In our unit at the Massachusetts General Hospital, we are spending much time on research in child psychiatry. It is a difficult field. The first thing one has to do is to limit the study to a concrete problem, such as is done in any other field of metabolic research, concerning which one's present knowledge gives promise of acquiring objective new information.

In closing I should like to emphasize the point that psychiatry is new. Psychiatry needs research, and research in child psychiatry is no easy matter. Let us devote our energy and time to developing this important field. As new knowledge is acquired pediatricians will be eager for it.

Dr. Harry H. Gordon, Denver: Without gainsaying the value of the concepts discussed, I find a practical problem arises: How can one introduce care of this quality into an appointment system, in either a clinic or a private physician's office, which allots fifteen minutes or less for the consultation with a child and a parent? Dr. Roberts has already indicated the value of ancillary workers and we have had a great impetus from army experience toward the use of group therapy, at least in clinical practice.

About two months ago, Dr. Lee Forrest Hill came to Denver to address a group of physicians, both general practitioners and pediatricians. In public at least, he did not discuss the American Academy of Pediatrics survey of child health service or its Committee for the Improvement of Child Health. I dare say that in private he did a great amount of spadework. In any event, he gave us much information on what a pediatrician can do along the lines of mental hygiene in his private office. I should like to suggest that he be called on for comment on this subject.

Dr. Lee Forrest Hill, Des Moines: I am much interested in the responsibility which practicing physicians, both pediatricians and general practitioners, should assume in attempts to guide parents in the rearing of their children in order to prevent later psychologic problems that might require the services of the psychiatrist. If preventive mental health is to be made available to the millions of children throughout the nation, it is incumbent on this group—pediatricians and general practitioners—to inform themselves about child behavior so that they in turn may interpret it to parents. There are little everyday things that parents need to know in advance if later, more difficult problems are to be prevented.

In my talk at Denver, to which Dr. Gordon referred, I discussed the behavior patterns common to most infants in the first two years of life and emphasized the importance of the physician's taking a few minutes in each preventive check-up examination to advise the parents on the type of behavior which might be expected in the period ahead and the way in which the various situations should be met. Especially helpful is this procedure when the mother leaves the hospital with her new baby and again at the beginning of the second year.

The first year, after the first two or three months, usually is not so bad for most parents. The baby stays in his bed or in his playpen and usually eats well, and, in general, mother has a rather easy time. But in the second year, when cerebral development has progressed to the point where he has ideas of his own and when motor development has progressed sufficiently for him to try to put his ideas into effect, the mother frequently has a bad time of it. It is during this year that behavior attitudes, desirable or undesirable, are in their formative stage, and some advance information to the parents may be helpful in establishing the more desirable ones. It seems to me important that general practitioners, who take care of 70 per cent of the children, also be sufficiently informed to give parents reliable advice in the preventive phases of child psychiatry.

Let us consider an example or two. The eating problem, so common in the age period between 2 and 5 years, not infrequently has its inception shortly after the beginning of the second year. Not only does the baby's appetite slow up in keeping with his decelerated rate of growth, but he makes his first attempts at self help. He tries to feed himself with his hands. He gets food in his hair and on the floor. It is a messy performance. A natural reaction on the part of the mother is to move the food out of the baby's reach or to spank his hand. I have even known a mother to restrain the child's arms so she could get a straight shoot at his mouth with the spoon. Add to this the apprehensive or overconscientious mother who coaxes or forces food on the baby when he does not want it and does not need it, and all the ingredients of an eating problem are present. Father, grandmother or even auntie is likely to take a hand. The baby becomes conditioned against the whole business of being fed. Mealtime is an ordeal for everyone.

Forewarning of parents of the likelihood of a slowing up in appetite and of the baby's self-feeding attempts, which should be encouraged rather than discouraged, plus a warning that forcing, coaxing and urging should not be done, usually results in an infant who has taken over the whole job of feeding himself by 1½ years of age. Thus, so simply for both parents and child can be prevented one of the unpleasant experiences common in the preschool child.

The problem of toilet training can be similarly approached. In this parent-physician conference near the first birthday, parents should be advised of the dangers of too early and too vigorous attempts at complete training before the child is sufficiently matured to be interested in seeking a place to deposit his stool or urine. Many infants do not arrive at this stage before 18 to 20 or 22 months of age. It should be pointed out to the mother that her task then is to teach the child how people use toilet seats rather than to run a race to see how many urinations and how many bowel movements she can catch in the toilet. The customary procedure is for the mother to carry the child to the toilet, remove his pants, place him on the toilet herself, see that he sits there, wipe him when he is through, lift him off, put on his pants and let him go. The mother is trained beautifully, but the child is being taught little or nothing about self responsibility in the use of the toilet. A more rational approach is for the mother to assist the

child as little or as much as is necessary but always with the insistance that he do as much as he can for himself. A number of children in my practice of 2 years of age are entirely independent of adult aid in going to the toilet. It can be done if parents can be persuaded to take the necessary time to teach the child rather than to do it all themselves because it is quicker that way and they are then free to go about other tasks.

Parents should also be warned that sleep disturbances frequently begin around the end of the first year. By this age most infants can pull themselves to their feet and stand by holding on. When the baby is put to bed, this newly acquired ability is tried out, accompanied with vigorous shaking of the side of the bed and vociferous demands to be taken back into the family circle. If he is indulged, or, more serious, if he is taken into bed with the parents, a habit is begun which inevitably increases in frequency and parents may not know a peaceful night for many a month. Faulty sleeping habits which start in this manner can readily be prevented, provided parents are properly alerted. Parents should be advised, too, that temper tantrums are to be expected in the period of 1 to 3 years, and the treatment is not to throw water on the child, to put him to bed, to spank him or to shut him in a closet.

I have singled out the second year to illustrate the point I want to make, but it is no less important throughout the period of growth and development, from birth through adolescence, that physicians responsible for the medical care of children anticipate for parents and interpret to them what may be expected in the way of normal child behavior in the various age periods.

DR. MITCHELL I. RUBIN, Buffalo: I have been interested in the subject of preventive mental hygiene since 1930 when, before entering the practice of pediatrics, I thought I should obtain some special experience in the field of psychiatry. After a two hour interview with a group in charge of psychiatry at a particular institution, I was convinced that with the complicated terminology in vogue it was not a field I should undertake too lightly, certainly not until I had become well grounded in terminology. In fact, it seemed to me I had better stay in somatic pediatrics.

I suffered a second major frustration in relation to child psychiatry when, after making provisions for this division at the Children's Hospital of Buffalo, my colleagues and I were confounded by the size of the total problem we faced in regard to the number of children who need special study and treatment and the establishment of a proper attitude toward mental hygiene in medical students, house officers and the rest of the staff of the clinic. Requests poured in from social agencies and the various schools for our help. I should like to outline briefly some of our meager efforts at solving a few of these many problems.

As was pointed out in the various surveys, the major number of children are cared for by general practitioners and it, therefore, seemed to us that our efforts should be in a large measure directed toward teaching this group of physicians, both potential physicians (students) and those in practice. In other words, we thought we should lay the major emphasis at what might be called the grass roots of the problem in child psychiatry. It is our experience that the medical student rarely has anything but an organic approach toward illness in children. He comes to us well prepared in biochemistry, pathology and the like, and it becomes our problem to establish a milieu where he can incorporate into his somatic thinking such factors as the social, emotional and psychologic aspects of the child. We geared our program largely to bring about this attitude. Dr. Sherman Little, who is in charge of our program, has attempted to give the

student an understanding of the mental hygiene aspects of child care, not as something added to his pediatrics but as something which must be integrated into everything he does for the child. Dr. Little works in the outpatient department several afternoons a week as a pediatric instructor to the students. He reviews the medical side of the problem with the students, the history and the results of physical examination, and, at the same time, brings to the student his special field of mental hygiene. Thus, the student receives the training painlessly. The social service department of the hospital has also been integrated into the program of attempting to make the student aware of the child as a member of a family and the community and of the bearing this has on his personality and behavior.

For many of the students six weeks' exposure to this type of program seems not enough to establish even a proper attitude, for, as Dr. Putnam has remarked, some persons have a "natural" aptitude for this approach in medicine, while others are so involved with their own emotional problems that they have great difficulty in understanding the problems of other persons and are unable to help them. Thus, it is required that the training program be highly individualized for each student and house officer. In the case of the medical house officers the majority of them, over a period of a year, do become indoctrinated. However, it is impossible in the case of the student who offers resistance to this type of thinking to do much in the short period of study offered. This aspect of the problem, however, must be faced and conquered, for the students are the practitioners of tomorrow who will care for the vast majority of our children. We have instituted a similar approach in our short refresher courses given to practitioners in the state of New York. We hope that in the two week period they are here for the course they can acquire this attitude.

DR. ALTON GOLDBLOOM, Montreal, Canada: I should like to enter this discussion briefly, as a pediatrician, not as one who can claim any training in psychiatry but rather as one who has been, like every practicing pediatrician, exposed at all times to problems which have a psychiatric side, who has learned that every problem presenting itself to a physician has psychiatric overtones.

This concept has been recognized for ages. My revered teacher, Dr. L. Emmett Holt Sr., used to say repeatedly that pediatrics was divided into three parts: the treatment of the disease, the treatment of the child and the treatment of the parents; thus, he, too, and many others before him, recognized how important that aspect of medical practice is.

At present words and form are being given to that which we, perhaps, have known for many centuries. There are in the Scriptures, there are in the writings of Aristotle, there are in all literature materials which are applicable today and which we can use successfully in illustrating the psychiatric phenomena of children. My pet book on child psychiatry, Herbert Spencer's essays on "Education: Intellectual, Moral, and Physical" (1861), I think contains more meat for practitioners and for psychiatrists than almost any book written before or since.

In the consulting room one always observes the disposition of the patient to talk and one is often conscious of one's own indisposition to listen. It is the development of patience that is perhaps the greatest virtue of the physician, and, if he is to deal at all with problems involving the psychiatric care of his patient (and much of that we call psychiatric care of patients seems to be related to the psychiatric problems of the parents), then the physician's consulting room must become in a sense a confessional. How much that idea exists, perhaps, is more in evidence to one who comes from the Province of Quebec than from anywhere else. This is predominantly a Catholic province, as you may know. The number

of times English Catholics address me, "Yes, Father," and "No, Father," or the French as, "Oui, mon Pére," has impressed me with the identification that patients make of a father confessor with a physician, and this impression has guided me in many of my actions.

DR. ALFRED H. WASHBURN, Denver: Among the other things I enjoyed in Dr. Powers' delightful paper was his quotation from Francis Peabody, who was an old hero of mine, that the important thing in the care of the patient is in caring for the *patient*. I wonder whether one should not at least add that the study and the learning of child psychiatry is the study of the child. I was much impressed with the reactions I obtained from some of the residents we received from Dr. Gordon's pediatric department for, shall we say, some exposure to our study of people in the Child Research Council. I should like to tell you one recent experience just to reenforce some of the things Dr. Putnam said about the need for actual experience with the growing child and with his parents.

We were discussing at one of our staff conferences a 10 year old boy who was obviously having a great amount of difficulty, anxieties, worries, aggressive behavior, poor marks in school, a whole string of difficulties. In the history, accounts were given of the mother's care for this child from a couple of days after birth until the present age of 10 years. They included the carrying out of six minor and two major operations, the giving of thirty-eight different drugs during various minor illnesses and many other evidences of the attitude of the mother. At this point, the psychiatrist on the staff made the remark that he had seldom seen a more beautiful example of punitive action, the aggressive punitive reaction of a mother toward a child, coming out frequently through the pediatrician's therapy.

The pediatric resident almost gasped in surprise. He had been with us only a month at the time, and he said, "I should have thought she was a perfect mother, with all that therapy."

I think that stresses the fact of our need to teach the young men going into pediatrics, as Dr. Putnam said, an awareness of the mother's behavior, the parents' behavior and their worries and an awareness of the way to interpret that sort of thing, so that they will not allow themselves to be used as instruments for such a mother's punitive action on the child.

No one has mentioned my second point, the need for better teaching of our embryo pediatricians before they actually get into pediatrics—the orientation of all students of medicine in relation to this whole problem of understanding people. It seems to me much can be done, not simply in the mechanics of changing curriculums, but in getting into the first year of medical school training teachers who are really great teachers, who have an awareness of this field. They should, from the first week of medical school, give these youngsters an awareness of, as I like to call it, medicine as "human biology" and an awareness of the fact that we are dealing not simply with bones and muscles, and later on with diseases, but with human beings.

We have been trying in Denver this year to start the beginning medical students with the dissection of newborn cadavers, showing them the difference between the small beginnings of life and the adult. We try to carry them through that first year with the best teachers in the school from the department for the study of human growth (i. e., the Child Research Council), the Department of Medicine, the Department of Pediatrics, the Department of Public Health and the Department of Rehabilitation, utilizing the best teachers, as far as we can, to talk to the students all the way through the first year on what people are like.

I think there is a great need, as we consider the problem of teaching physicians, for being more aware of the men we are talking about and their beginnings back in the medical school stage of their learning, remembering that a great many of the children and their parents are going to be looked after by general practitioners and not by us pediatricians.

DR. RALPH V. PLATOU, New Orleans: I question the rôle of one way vision technics as they are ordinarily employed in pediatric or child guidance clinics. I have had a relatively brief experience with such technics. It seemed to me that the emotional trauma that may result, whether or not the patient or the parent is forewarned, may be serious. I raise this question, not critically, but from the point of view of possible unpleasant aftermaths and for the purpose of asking discussion from one or several of the essayists concerning their own reactions to these technics.

DR. MARION C. PUTNAM, Roxbury, Mass.: We have not used our one way vision screens nearly as much as we had expected. They are useful for the initial stage of the "social introduction" of the students, whether they are visiting from medical schools on the outside or are our own trainees, to acquaint them with the teacher and with the children in the groups, without their feeling too strange by being in the room. Actually, we find that from the standpoint of making observations the psychologic separation of the screen and the process of sitting still while there is activity on the other side of the screen seem to inhibit the making of detailed and sensitive psychologic observations. We quickly abandoned the use of the screen and encouraged the pediatrician to go in and help directly with the children. In that way, they "get the feel" of the behavior of the children which is difficult to get through the screen.

I do not think we have had any unhappy experiences with our screens. We do not keep them particularly secret. The children know persons are behind the screen. They pay no attention to it any longer. It has been fairly useful for mothers who sometimes find it difficult to separate themselves from the children and who can do so if allowed to observe through the screen. We have used it when the pediatrician in training, for instance, has had some direct experience in therapeutic work with young children. It sometimes is useful to enable him to observe an experienced child psychiatrist in a treatment session with a child. But for children receiving intensive treatment who care so much about being alone in the room with the psychiatrist, I agree with the speaker that it can be disturbing to have somebody behind the screen.

DR. HILDE BRUCH, New York: This discussion shows how well psychiatry and pediatrics can be integrated. I was particularly grateful for the few case examples which were reported. Those of both Dr. Washburn and Dr. Weech illustrated how well the pediatrician can recognize basic emotional problems of the parents from the information they give at the time of regular office visits.

Effects of Large Loads of Electrolytes. DR. J. L. GAMBLE, DR. W. McL. WALLACE, DR. L. P. ELIEL, M. CUSHING, J. APPLETON, A. SHENBERG and J. PIOTTI, Boston.

Effects of additions of several salts to the food intake of healthy infants were separately observed with the purpose of determining (1) the lag in removal of a large load and extent of the accumulation of electrolytes in the body, and (2) the effect of gain to the body of extracellular electrolytes on the balance for intracellular electrolytes and vice versa. The relevance of the findings to parenteral administration of fluid therapy is discussed. Obstacles to accurate measurement of the balance of extracellular electrolytes are also considered.

Multiple Births in the American Colonies. Dr. Ernest Caulfield, Hartford, Conn.

Boston town records from 1660 to 1729 revealed 163 pairs of twins among 15,797 known confinements, or a ratio of 1:96.9. The latest published ratio in the United States (1940 to 1944) was 1:95.8.

It is estimated that 500 sets of triplets were born before 1775. Records of 89 sets have been found, mostly in colonial newspapers. Other sources yield enough additional information to make the statistics on 50 sets fairly complete. The youngest mother was 18 years of age, the oldest "near 50." About one third of the mothers were between 36 and 40. About one third had twins in addition to triplets. One-half had been confined five or more times. Of 34 mothers whose exact death records are known, 3 died within a month and 3 more within a year. There were 18 sets of boys, 19 sets of girls and 31 mixed sets. There were 103 boys to 101 girls. Neonatal mortality was about 50 per cent, infant mortality about 60 per cent. About 25 per cent lived to be adults. At least 8 sets of quadruplets were born between 1742 and 1775. Quintuplets were born in Lake George (town) in 1808.

Adjustment of Electrolytes and Water Following Premature Birth. Dr. Clement A. Smith, Dr. Simon Yudkin, Winifred Young, Dr. Alexandre Minkowski and Margaret Cushman, Boston.

Premature infants at the Boston Lying-In and Children's Hospitals are given no water or food for two to four days after birth. Although this period is referred to later as one of dehydration, the loss of body water may actually be advantageous to the infant. Measurements of water, electrolytes, urea and total nitrogen were made on complete collections of urine during this phase. The results throw some light on the degree of physiologic limitation of renal function at premature birth. Balance studies made during the period of feeding immediately thereafter indicate the temporary or permanent nature of adjustments made while fluid was withheld. Such data, with appropriate studies of blood samples, offer a basis for evaluating the water and electrolyte status of the fetus at the time of premature birth.

All infants thus far investigated have shown (*a*) loss of both intracellular and extracellular electrolytes during the "dehydration" phase; (*b*) rather uniform ability to conserve water by concentration of urine (though not to adult levels), and (*c*) an outgo of nitrogen disproportionately less than that indicated by potassium loss from tissues. No rigid pattern of removal and restoration of electrolyte, water and nitrogen has emerged. Instead, the infants have displayed either of two different patterns. One of these is marked by early loss of large amounts of sodium, water and nitrogen. The infants of this group either reaccumulate sodium slowly after feeding is begun or may even continue in negative sodium balance. Infants in the other group show much smaller losses during "dehydration" and their pattern of reaccumulation includes more rapid replenishment of sodium. There was no apparent relation between fetal age and the performance of the infant as shown by these data.

DISCUSSION

Dr. Clement A. Smith, Boston: Actually, we would have much preferred using full term infants for observations of this sort. One would really like to know similar facts about the readjustment of the 95 per cent of infants who are born at full term rather than the facts we did obtain on the 5 per cent who are born prematurely. We still hope to get such data and we desire them greatly.

I was extremely surprised when these few infants showed such profound variations in the amount of water they were prepared to get rid of and in the proportions of their rejection of accompanying sodium. The data from the literature by Iob and Swanson (Am. J. Dis. Child. **47**:302 [Feb.] 1934), and recently by Flexner and others (*J. Pediat.* **30**:413 [April] 1947), indicated that we should have observed simply a higher proportion of water and sodium in the body at birth to about the same extent in all babies. This indicates that unless many infants are studied one cannot be aware of the amount of variation.

The clinical appearance of edema in these infants was not always immediately noted and required close observation, but the estimate whether the baby was edematous or not was made in every case before, rather than after, the laboratory data came through. I have no idea why some of these premature infants are so edematous and so overloaded with water and the accompanying electrolytes, and we shall continue to seek the answer to that. The omission of water, which in the opinion of Dr. Stewart H. Clifford is clinically justified, seems to us reasonably safe in most infants and is perhaps a good procedure in the more edematous ones. It is, I should say, fortunate that the infants in whom one is most inclined to continue omission of water for several days, or for more than two days, are obviously the ones who are wetter at birth and who will reward one by putting out excessive amounts of water as well as sodium; therefore, with a little clinical guidance it is quite safe to manage premature babies in this way and obviously it avoids certain dangers of aspiration.

Dr. Irvine McQuarrie, Minneapolis: Will you tell us what the mechanism of edema is?

Dr. Clement A. Smith, Boston: I do not know. It seems obvious from these charts that the edematous babies have an excessive amount of sodium and chloride and of water to keep these isotonic in the body, but why that should be so I do not know, and which comes first I do not know. As Dr. Yudkin said, edema does not seem to be related to the maturity of the infant, or to anything outstanding in the obstetric history.

Dr. Irving McQuarrie, Minneapolis: Is serum protein a factor?

Dr. Clement A. Smith, Boston: We would like to make it clear that the serum proteins are not consistently lower in the edematous than in the nonedematous infants.

Dr. Mitchell I. Rubin, Buffalo: Dr. Smith in his presentation said he did not have the opportunity of studying full term babies. While doing mannitol clearances in our laboratories, we were able to estimate what might be called the "mannitol space" (probably not the true interstitial fluid space). In a group of babies between the ages of 2 and 22 days the mannitol space averaged 29.3 per cent of the body weight, with a range of from 19 to 40 per cent.

Dr. Simon Yudkin, Boston: My only regret is that I personally will not be able to continue these studies, because they seem to have opened a field which presents new data that look interesting, especially endocrinologically. I do not know whether the endocrinologists here would like to comment on the possible relationship of these changes to fetal adrenal cortex, but that was just one possiblity. Certainly there are many questions raised by these data which need further study.

Dr. Daniel C. Darrow, New Haven, Conn.: The discussion on phychiatry this morning reminded me of what Toynbee calls "withdrawal and return." I think psychiatry has been withdrawn from the pediatric clinic and is now

returning. During the period of withdrawal, theory and technics were developed which will now be applied to pediatric problems. I believe the results will surprise psychiatrists and pediatricans with facts that both fit in with and are discordant with psychiatric theory. We probably shall witness a psychiatric renaissance.

I think the studies on balance techincs illustrate the same principle: that is, students of water and electrolyte metabolism have withdrawn from the clinic. At least I know I have personally been studying the phenomena in experimental animals, and this work together with similar studies by others has developed new theory and technics which enable us to apply the old method of determining balances with more insight than we formerly had.

The estimation of balances, as Dr. Gamble has pointed out, is full of difficulties which we have not altogether overcome. The troubles arise from the inability to get accurate balances. The errors probably are connected with losses through the skin which will have to be precisely measured. Our theory permits a more precise interpretation than the accuracy of our data warrants. The accuracy of the data can be checked by our ability to reconcile the findings with analyses of tissues in experimental animals. The papers of Dr. Gamble and Dr. Yudkin show reasonable approximations to changes which have been demonstrated in experimental animals.

Dr. Yudkin showed me the data from balances during the newborn period in one baby. It fascinated me to find that the exchange of sodium for potassium in the cells was about two thirds of a milliequivalent of sodium for one of potassium. Dr. Gamble's data show a similar relation. This is the relation for exchanges in certain experimental animals.

As my associates and I pointed out in a recent paper in the *Journal of Clinical Investigation* (**27**:198-208 [March] 1948), we cannot expect to find this relation under all conditions. We do not know in which circumstances this relation will not hold, but I think that the relation will not be found when there are multiple deficits of electrolyte which make it impossible for the kidneys to maintain the usual adjustments of body water and electrolyte.

Dr. Irvine McQuarrie, Minneapolis: This interesting report by Dr. Gamble and his associates on the over-all balances of water and electrolytes indicates that the electrolyte patterns of the several compartments may be greatly distorted temporarily under conditions of excessive load. The data presented appeared to me to show that even in extreme conditions water still continues to move with sodium, so long as this ion is present in sufficient amounts. On the other hand, Leiter found some years ago that, in a state of sodium depletion, water may be retained in the extracellular space with administered potassium.

In some disease states, especially in certain endocrine disorders, intracellular electrolyte patterns deviate considerably from the normal. One would assume that under such conditions responses to the administration of a given solution vary accordingly. As indicated by some recent studies involving analyses of brain, liver, heart and skeletal muscle of normal growing rats, the several organs behave differently with respect to experimentally induced alterations in their water and electrolyte content. For instance, the daily injection of comparatively large doses of desoxycorticosterone acetate for seven days or longer was found to cause a decrease of 20 to 25 per cent in the potassium content of the brain and skeletal muscle, with only a minor fractional replacement by sodium and no significant change in the water and chloride content. Heart muscle, on the other

hand, showed no significant decrease in potassium content. At the same time, the liver showed a 30 per cent loss of this element. Prolonged insulin hypoglycemia resulted in changes almost diametrically opposite those induced by the sterol.

Thyroid Deficiency as a Factor in the Development of Celiac Disease.

Dr. J. A. Johnson and Dr. P. J. Howard, Detroit.

The possible role of thyroid deficiency as an underlying factor in the development of celiac disease is discussed on the basis of the following types of evidence: 1. The known defects—diminished absorption, altered motility, retarded bone age—have all been demonstrated in hypothyroid states and shown to be reversible by the use of thyroid. 2. A case of refractory tetany complicating celiac disease was studied with the balance technic, and it was shown that a negative balance could be rendered positive by treatment with thyroid. 3. Another subject with retarded growth and the symptoms of celiac disease was studied in a similar manner and showed a correction of the calcium storage defect with thyroid therapy.

It is obvious that, since so few cases of hypothyroidism show evidences of celiac disease, this can be but a single factor in its causation, and it is our concept that other factors blamed—chronic lymphoid infection, allergy—become trigger mechanisms only when superimposed on this conditioning factor.

The material consists of a review of 52 cases of celiac disease and of 17 of pancreatic fibrosis. The normalcy of bone plates in the latter condition is offered as a further argument against accepting the well known bone picture in celiac disease as a result of the nutritional disturbance rather than as an etiologic factor.

DISCUSSION

Dr. Nathan B. Talbot, Boston: This ingenious presentation raises interesting questions. First, is there evidence that thyroid deficiency in children leads to true steatorrhea as determined by quantitative measurements of fat absorption?

The second question concerns Dr. Johnston's remarks at the end of his paper. As we have watched hypothyroid children, many of us have had the feeling that children with a primary disturbance of the thyroid gland resulting in lack of the thyroid hormone ordinarly present a fairly clearcut and readily distinguishable clinical picture. This is the picture commonly described in textbooks and characterized by stunting of growth, retardation in skeletal maturation, epiphysial dysgenesis, lack of energy, sometimes mental sluggishness, coarse dry skin, constipation, cold hands and feet and the like. In contrast to this picture is that presented by children with functional hypothyroidism secondary to a decrease in production of the pituitary thyroid-stimulating hormone. In this circumstance, perhaps because the hypothyroidism is of mild degree, signs of lack of thyroid are apt to be quite subtle. Of the aforementioned signs only stunted growth, retarded skeletal maturation and, at times, epiphysial dysgenesis are in evidence. Such pituitary types of thyroid deficiency may be due to an organic lesion in the anterior lobe of the pituitary gland or to functional or homeostatic changes in the activity of the anterior lobe. Malnutrition may be an authentic cause of such a functional type of deficiency of the pituitary thyroid-stimulating hormone.

One way of distinguishing between primary and secondary hypothyroidism is to observe the effect of thyroid therapy on the growth rate. It has been my experience that children with primary thyroid lack grow at least 6 cm. during the first six months of replacement therapy. By contrast, children with the pituitary or secondary type of hypothyroidism ordinarily fail to undergo such a growth response. Would Dr. Johnston comment further on the growth response of his patients to thyroid therapy?

DR. J. A. JOHNSTON, Detroit: I do not mean to leave the thought that hypothyroidism is the cause of celiac disease, but that these data suggest it constitutes the underlying metabolic defect on which celiac disease is superimposed if one adds the trigger mechanisms of infection, allergy or emotion. These items in themselves do not seem to us adequate to explain celiac disease except when they occur in someone whose underlying metabolic flow makes a normal protective response impossible. Many analogies will occur to you. The well fed child with adequate protein reserves and adequate tissue does not respond to diarrhea by dying; he adjusts to it; his ability to respond is intact. But when severe diarrhea occurs in an atrophic child the story is different, and attempts at therapy are met by an inability on his part to respond. Lack of ability to respond is what characterizes, among other factors, the child with an abnormal metabolism. Even when a depressed metabolism is not directly due to thyroid deficiency but has occurred as a result, say, of prolonged rest in bed, we have been able to show that the diminished storage of nitrogen and calcium associated with this can be corrected by raising the metabolism with small doses of thyroid; larger doses become catabolic. I should qualify all that I have to say by pointing out

Adjustment Ratings of 226 Children with Reference to Physical Condition During the First Two Days of Life

	Good Physical Condition (73.9% of Children)		Poor Physical Condition (26.1% of Children)	
	Number of Cases	Percentage	Number of Cases	Percentage
Good adjustment	104	62.2	25	42.4
Medium adjustment	31	18.5	11	18.6
Poor adjustment	32	19.2	23	39.0
	167	100.0	59	100.0

that Detroit is in the goiter belt, and that possibly we get an exaggerated idea of the frequency.

Paranatal Factors Affecting Adjustment in Childhood. DR. STUART SHELTON STEVENSON and DR. HAROLD C. STUART, Boston.

In an attempt to determine those paranatal factors which may affect adjustment in childhood, 226 children were studied. These children were followed in connection with a longitudinal study of child health and development; accurate, extensive data are available concerning their mothers' obstetric histories, their neonatal periods and their mental and emotional characteristics.

Their general physical conditions during the first two days of life were evaluated as "good" or "poor"; these ratings were made without reference to other than neonatal data. Their general adjustments to their environments up through at least 5 years of age were also rated independently, as judged by the progress notes of psychologists, pediatricians, social workers and nurses and by parents' comments concerning the children. Data concerning the child's gestation, birth, neonatal period, intelligence and family situation were then studied.

The table shows a highly significant relationship between childhood maladjustment and poor physical condition in the first days of life. When such factors as toxemia, primiparity, long labor, abnormal delivery, prematurity, twinning, cyanosis during the first twelve hours of life, need of resuscitation or an appreciable

interval between birth and establishment of respiration are tabulated, it is found that each of these factors results in an increased incidence of children who are in poor physical condition in their neonatal periods. However, the relationships shown in the table are maintained to varying degrees in the presence of each of these factors. This suggests that any of the factors may be responsible in part for the physical condition of the newborn infant but that no one of them alone is critically causative of childhood maladjustment.

First-born children and only children show a greater incidence of maladjustment following good physical condition in the first days of life, as is to be expected. However, even within these two groups of children, the relationships shown in the table are maintained. The percentage of children in good physical condition in the neonatal period decreases slightly as the intelligence quotient decreases, but again the relationships of the table are maintained at different levels of intelligence.

Among the 226 children were 92 siblings in 41 families. There was no consistency of neonatal conditions or childhood maladjustment within a given family group. This suggests that environment was not a major factor in determining the adequacy of their adjustment.

It may be concluded that the child's physical condition during his first days of life may affect his adjustment in later childhood and that several paranatal factors may influence this physical condition. It is to be hoped that these factors may be studied with a broader perspective for their possible effects beyond the first days of life.

DISCUSSION

Dr. Harold C. Stuart, Boston: Dr. Stevenson has shown positive correlations between good ratings and poor ratings on two dissimilar types of data obtained on the same children at widely different periods of time. The interpretation of any such association involves many complicated problems, certainly must be guarded at this time and requires much further study along various lines.

It is always difficult to make precise and repeated observations of a number of different types on the same persons over a period of years. There are usually many unknown and uncontrollable variables which may have had a part in leading to the association found. Items dealt with are not always specific or easily rated precisely, so that planning research to further an understanding of this kind of relationship calls for much thought, and the actual study must be carried out with great care.

Some of the difficulties which are involved in such plans were shown in Dr. Stevenson's second slide in regard to the abnormal deliveries in this series. As the material on this slide was complicated, I remind you that there were 28 such deliveries in this group. Half the babies who experienced an abnormal type of delivery—13 of the 28—were in good physical condition at birth and presumably had not suffered damage as a result of this experience. Only 1 of the 13 in good condition, or 7.8 per cent, was rated as poorly adjusted in early childhood. In contrast, 8 of 15, or 53.3 per cent, who showed signs of being in poor physical condition at birth were poorly adjusted later on. This difference is striking. Does it occur by chance? It does not seem probable in view of the statistical evidence. Is it an indication of persistent structural changes resulting from central nervous system damage at the time of delivery? Is it due to physiologic effects on the fetus of the maternal condition which led to the abnormal delivery? (Six of these abnormal deliveries were associated with toxemia.) Is the correlation due to differences in the early management of the infants, brought about

either by the mother's own condition or by her concern over the neonatal difficulties? Is it due to so-called psychic trauma from the baby's condition or experiences in his early days?

Obviously these questions cannot be answered on the basis of the evidence at hand. It is important from many points of view, however, to consider the possibility of there being an anatomic factor involved in some of these instances. It seems unlikely that the final answer to any of these questions could be a categorical yes or no.

The immediate problem for research is to obtain further evidence which will indicate the relative importance of the different factors mentioned. The influence of this study on infant care at this time should be to make obstetricians and pediatricians aware of the need for closer and more continuous observation of infants who have been born in abnormal circumstances.

Dr. Milton J. E. Senn, New York: This paper reminds me of one of the statements made in discussion earlier by Dr. Allan Butler. He said that research in child psychiatry is proceeding apace with developments in pediatrics but is a most difficult endeavor. One of the difficulties is that each method of study needs careful planning, with concern for all those things which interest every person doing research, yet which in the field of psychiatry and the social sciences are most difficult to control.

One point lacking in this paper is a statement of standards by which the adjustment of the children was rated poor, medium or good. It is true that subjective factors come into play in a classification of people, as the authors point out; but even though such errors may be eliminated in part by having the diagnoses shared by a battery of investigators—in this study a group made up of nurse, psychologist, pediatrician and parents—it would be well to include the data on which the classification was based.

It is important to know at what period developmentally the children in this study were rated; in Dr. C. A. Aldrich's presentation some of the "normal" children showed behavior characteristics of the developmental period of 2 to 2½ years of age, yet the behavior resembled that of some of Dr. Stevenson's "problem" children. The presentation of developmental data would have added to our understanding of these children. Dr. Aldrich, Dr. Washburn and all of us engaged in longitudinal studies of growing children realize that individual children vary considerably, that every healthy child probably is poorly adjusted (by somebody's standards) at one time or another in his life. For these reasons I should like to emphasize that in research in child psychiatry, as in other research, we need appraisal of methods and careful consideration of standards when behavior is described as deviant or abnormal.

Dr. Bronson Crothers, Boston: I am fascinated and baffled by this paper. I like the prefix "para," but I do not quite know how the authors use it.

At various times the question of whether there is a typical pattern of behavior after damage to the nervous system has been considered. I remember one period when it was assumed that the children who had had encephalitis or cerebral trauma would be intelligent, overactive and uninhibited. At that time we saw a series of children who followed the specification without injury or infection preceding this behavior. Moreover, we have followed many children after known infection or trauma who did not exhibit the predicted syndromes.

This study is certainly better than any I know about, since it starts at the beginning of life and is based on serial observations. I think the validity of the conclusions depends on the adequacy of the psychologic investigation. If psychologic

appraisal is confined to psychometry and does not include strictly all the psychologic deviations which occur without significant changes in intelligence quotients, the conclusions are vulnerable. This seems to me an important paper, but the conclusions are admittedly tentative.

DR. STUART S. STEVENSON, Boston: The word "paranatal" has been used in the sense intended by Schreiber, to designate factors which may be operatitve before, during or just after birth. Intelligence quotients were obtained for these children from the ages of 3 months to 5 to 8 years. There were never less than five intelligence quotients, I believe, recorded for any one child and those presented here are average of all the intelligence quotients which were recorded. I should add that the intelligence quotient was only one of several approaches used in the psychologic appraisal of these children and I agree fully with Dr. Crothers about the limitations of this index.

A child was considered maladjusted if his behavior was consistently inappropriate for his age. If a child showed temporary behavior difficulties within a few months' period or a few weeks' period, he was not called maladjusted, provided his over-all picture seemed normal. The type of child we considered to be maladjusted was consistently so at all ages. His behavior seemed to deviate from normal, frequently from the time of the first observations; he was often the kind of child who did not get along well in school; the kind of child who was in more or less constant trouble with his family and the neighborhood; the kind of child who was a feeding problem in infancy—the one who presented a fairly consistent picture of difficulty in getting along with his environment.

DR. HAROLD C. STUART, Boston: Dr. Stevenson did not have an opportunity to explain who participated in the collection of the records which he evaluated. During all this period of eight years we had two psychologists studying these children. One of these, Dr. Psyche Cattell, was concerned primarily with intelligence tests and ratings on various scales; the other, Dr. Mary M. Shirley, was in charge of an observation nursery school to which these children were brought for a period of weeks each year and in which the most detailed observations were made. Dr. Shirley is now deceased so that she did not rate her material personally. That is one of the many difficulties which arise in the long time study of children. Her records were complete and well summarized, however, so that it does not seem likely that they were seriously misinterpreted. We did not simply talk to the mothers and ask whether they thought their children were well behaved.

DR. BRONSON CROTHERS, Boston: The point I wish to make is that children can be seriously impaired without interference with the intelligence quotient. If the psychologist is limited to estimation of intelligence, many highly significant deviations are missed.

My feeling about this paper is one of admiration for the thoroughness of the authors, respect for their general method and hopeful skepticism about the durability of their conclusions.

DR. STUART S. STEVENSON, Boston: Dr. Crothers, I pointed out in my paper that children with low intelligence quotients as a selected group showed a higher incidence of damage at birth. However, the children presented here showed about the same correlation between good and poor conditions at birth and what we have called good and poor adjustment no matter what their intelligence quotients, although the brighter children, even when poorly born, seemed to get along a little better than the more stupid ones.

Basal Metabolic Rate in Obese Children. DR. HARRY H. GORDON, DR. ALBERTA ILIFF, Denver; HELEN MCNAMARA, New York, and DR. W. RANDAL BELL, Marblehead, Mass.

Systematic studies and clinical impressions are in agreement that obesity in children, as well as in adults, is caused by a functional disturbance of appetite regulation. Failure to find basal metabolic rates in obese children which conform with this view has led to confusion about the validity of observations. Five hundred and twenty-four observations of the basal metabolic rate of 348 obese children were made in New York and Denver. When the surface area–age standards of Lewis, Duvall and Iliff, as used by the Child Research Council, were employed, only 4 per cent of the obese children had rates below —15 per cent, as compared with 29 per cent by Mayo standards. Use of either weight or height as standards of reference introduced distortions of the data, the magnitude of which depended on the degree of obesity. For some unknown reason, the use of the surface area–age standards of the Child Research Council proved unsatisfactory as a standard of reference for the metabolic rates of dwarfs.

DISCUSSION

DR. BÉLA SCHICK, New York: For many years Dr. Anne Topper and I have been interested in the question of basal metabolism of normal, subnormal and obese children. We realized that most of the standards for obese children, particularly for those between 10 and 16 years of age, are unsatisfactory. The standards are based on the determination of the body surface (Rubner). This determination, accomplished by covering the surface with adhesive plaster or tinfoil or by submersion under water, is too complicated. Formulas were constructed based on weight and height, with corrections so that the resulting figures should become similar to the actually determined body surface. The standing height is always questionable. No one will put a horse on its hindlegs in order to measure the height. We do it in human beings without hesitation because we walk on two legs. As far as the basal metabolism is concerned, legs and arms are not involved. The basal metabolic rate expresses the chemical processes of the internal organs, the heart, lungs, liver, kidneys, spleen, and not of the muscles of the extremities and body. These muscles are at rest. Amputation or ligation of legs does not change the basal metabolism (Topper and Mulier and others). I am using the formula of von Pirquet, which is based on the sitting height. The latter has an interesting relation to the development of the body. In talking with Dr. F. G. Benedict about the various formulas, he told me that among all formulas that of von Pirquet is the most satisfactory. By squaring the sitting height (in centimeters, not inches), a value is established which, as von Pirquet realized, is not identical with the body surface but which satisfies the physiologic fact that the basal metabolic rate has to be calculated on a square and not according to a cube. The basal metabolic rate amounts to two decicalories per square centimeter of sitting height squared.

DR. JOSEPH A. JOHNSTON, Detroit: I should like to ask Dr. Gordon whether he made any comparison of his data against the predictions of the Wetzel grid. I did this in a series of obese children and found that the large obese child showed, as we might expect, rates that were 20 per cent higher than those found with the conventional standards for surface area.

DR. HARRY H. GORDON, Denver: Dr. Schick has touched on some important objections to the use of surface area as a standard. The first, as he pointed out, is the inaccuracy in measurements of surface area. One of the reasons for thinking

that there is validity in the surface area law, that is, that surface area has something to do with the rate of oxygen consumption, depends on consideration of heat transfer in the body. Since surface area determines heat loss, if we are to maintain a constant body temperature, it will also affect heat production. It has been pointed out, however, that the total surface area is not a fair measure of effective surface area with respect to heat loss; for example, the inner aspects of the thighs and the legs are not as important as the outer aspects and, therefore, we can expect only a rough correlation between total surface—even if we measure it exactly—and effective radiating surface.

This brings one to the possibility that the use of a surface area formula based on both height and weight and approximating the 0.75 power of weight has given good correlations clinically as a standard of reference for the basal metabolism only by chance. Kleiber has recently given an extensive discussion (*Physiol. Rev.* **27**:511-541 [Oct.] 1947).

We should like, however, to differ with Dr. Schick when he states that the standards are wrong. The standards are not wrong; it is our use of them which may be wrong.

In answer to Dr. Johnston's question, we have not compared these observations with the Wetzel grid. We are turning the data over to Dr. Edith Boyd, who is now working on a weight-height index which may be a more valid standard of reference for the basal metabolism.

Etiologic Factors in Celiac Disease. Dr. J. H. Ebbs, Dr. M. Thompson and Dr. W. O. Stein, Toronto, Canada.

It was observed that the 90 cases of celiac disease reviewed could be divided into three groups according to the type of onset. The first group followed a known acute or chronic respiratory infection, with a sudden onset of symptoms. The second group had no known infection but often included other possible factors. This was the idiopathic group with insidious onset. In a third small group the condition developed soon after birth and the disorder was difficult to differentiate from fibrocystic disease of the pancreas.

Celiac disease appeared, on the average, in breast-fed infants at 16 months of age and bottle-fed infants at 10 months. Children with the disease appear at later maternal ages than do their sibs without the condition, and late in birth order. Twin pregnancies were commoner than expected, and a history of diabetes in the family was frequent. These factors all suggest a possible disturbance of growth during prenatal life.

In uniovular twins the concordance for the celiac condition was present in 100 per cent and in binovular twins in only 50 per cent. The incidence of more than 1 case of celiac disease in a family exceeds the expected rate in the population, and the incidence in relatives suggests a recessive gene. The incidence of diabetes in a follow-up study of our children with the disease and the incidence in parents, sibs and grandparents suggests that all patients with celiac disease should be regarded as potentially diabetic.

Celiac disease seems to be a condition which appears only in children of the diabetic genotype and its appearance, being due to a recessive gene, is favored by late birth order, twin pregnancies, maternal diabetes or prediabetes, infections and improper feeding. By reproducing these factors in rats, with high fat diet and administration of streptococcus toxin and iodoacetic acid to replace the hereditary factor, we demonstrated in some litters of young rats the stunting of growth, enlarged abdomen, loose stools and clinical picture of celiac disease.

DISCUSSION

Dr. Paul Gyorgy, Philadelphia: If I understand Dr. Ebbs rightly, he has encountered in his material four times the combination of diabetes and celiac disease. This syndrome, including diabetes, steatorrhea, large liver and stunted growth, was described in France some years ago and is usually referred to as the Mauriac syndrome. Publications dealing with this apparent clinical entity appeared also from Switzerland, the Low Countries and Hungary. It is possible that the cases of Dr. Ebbs showing this combination of diabetes and celiac disease belong in the category of the Mauriac syndrome and represent the first relevant observations on this continent.

Dr. Clement A. Smith, Boston: I have been running over in my mind how many children with celiac disease and how many with diabetes I have seen, and I do not remember any association. The group in this room must have followed a great many children with celiac disease. It might be of interest if the chairman asked all those who have seen diabetes develop in children with celiac disease to put up their hands.

Dr. S. Graham Ross, Montreal, Canada: How many have seen celiac disease develop in diabetic children? [Six hands were raised.]

Dr. S. Graham Ross, Montreal, Canada: How many have seen diabetes develop in celiac children? [Ten hands were raised.]

Dr. Joseph A. Johnston, Detroit: I can verify something of what Dr. Ebbs says of heredity. A history of the disease was prominent in the siblings and even in the parents of many of the children we reported on yesterday. In regard to diabetic children the only instance I know of was the first patient referred for treatment twenty-two years ago. The child had been treated for celiac disease for two years but she was actually diabetic. She had a large abdomen, steatorrhea, glycosuria and dwarfism. Instead of a low flat dextrose tolerance curve, she had a typical diabetic one. The role of heredity was suggested in another patient who showed celiac disease at 1 year of age and ceased to have any symptoms from 2 to 3. Frank myxedema was evident at 5. The mother gave a history of a thyroid deficiency for which she was under treatment during pregnancy.

Dr. Béla Schick, New York: I agree with Dr. Ebbs concerning hereditary factors in celiac disease. I had a patient 3 years of age with celiac symptoms whom I healed with the usual diet and pancreas powder. Many months later the father, a physician, told me that he was having attacks of intensive diarrhea. As his child was healed with pancreas powder, he had the idea of trying it for his condition. At this time he is free from these attacks. We may conclude that his pancreas was not quite normal. In the history of the family, we will find symptoms supporting deficiency of the pancreatic function.

Dr. Edward A. Morgan, Toronto, Canada: My associates and I have felt for a long time that there is a fairly definite geographic distribution of celiac disease and it occurred to me that perhaps such a distribution of celiac disease might coincide with the geographic distribution of goiter. It would be an interesting subject to follow up, I think.

Bronchiectasis: The Segmental Distribution of Pathologic Lesions. Dr. J. R. Moore, Dr. S. D. Kobernick and Dr. F. W. Wiglesworth, Montreal, Canada.

In recent years there has been much interest in the resection of lung segments, as opposed to lobectomies, in the surgical treatment of bronchiectasis. Two important principles underlie the procedure of segmental lung resection: The first

is that bronchiectasis is not a progressive disease, or at least it has progressed as far as it will by the time the diagnosis is made and will not spread from segment to segment. The second is that it is primarily a segmental disease. If these assumptions are correct, there should be no histopathologic changes present in bronchographically and grossly normal segments. With these points in mind, we thought it worth while to make a study of the pathologic lesions in bronchiectasis in lung tissue by examining each segment in detail.

Our material consists of 7 cases of fairly early bronchiectasis in children for whom lobectomy, and in 1 child pneumonectomy, was performed by Dr. Dudley E. Ross. Lingulectomy was the only form of segmental resection used, and it was possible for us to study the gross and microscopic lesions in a fair number of segments, roentgenologically both normal and diseased. The lungs were dissected segmentally, and the nomenclature is that used by Dr. A. F. Foster-Carter.

The patients, of whom 2 were boys and the remainder girls, varied in age from 2 to 11 years. Their symptoms dated from one to eight years prior to the operation. In the gross appearance of the specimens no striking difference in the parenchyma between the involved and the uninvolved segments was observed. Ectasia was present in one or more segments in 4 children and was not demonstrable at all in 3. Histopathologically, the essential lesions were inflammatory in nature, with the lymphocytes and monocytes as the predominating cells, but a few neutrophils were present as well. The cellular infiltrate and fibrosis varied considerably from child to child and from segment to segment. The bronchial inflammatory lesions in our opinion became more and more pronounced as the bronchi became smaller. The major bronchi showed lesions which were not as severe in extent as those in the small bronchi and the bronchioles. Scarring was also more prominent peripherally than centrally. Lesions of the parenchyma (including that of the respiratory or transitional bronchioles and alveoli) were common.

From the clinical point of view, the roentgenologic diagnosis of bronchiectasis is the most reliable guide to the extent of the lesions. For all practical purposes, especially segmental surgical intervention, it is the bronchographic appearance, coupled with the results of the examination by the surgeon at the time of operation, that determines the extent of the operative procedure. The exact value of the procedure has yet to be proved. It is evident in our study that there are segments showing histopathologic inflammatory lesions in which no change was demonstrated by bronchography or on gross examination. The microscopic changes were similar in type to, but less in degree than, those seen in the segments which showed roentgenologic changes. The difference between the lesions of the dorsal segments and those of the basic segments appeared to be quantitative only. That extreme care must be exercised in the interpretation of the roentgenologic appearance in the selection of the segments for resection is illustrated by the fact that even the more advanced lesions are, on occasion, not accompanied with changes in their roentgenologic appearance. In basic segments, however, where bronchography has not demonstrated dilatation, we have observed lesions as severe as those in the incriminated segments.

In conclusion we wish to emphasize four points:

1. Destructive lesions of the bronchi, such as epithelial ulceration and destruction of muscle and elastica, were not a predominant feature.

2. Detailed microscopic examination showed definite, if minimal, inflammatory lesions of the bronchographically and grossly unaffected segments, but it is impossible to draw any conclusions about whether they are progressive or not.

3. The pathologic findings in this small series of patients have not been entirely consistent with the bronchographic appearance. This is understandable if the

ectasia is considered as a secondary phenomenon in which visible and definite involvement is not immediately present.

4. Such findings point to the necessity of further detailed study of the various lung segments from the clinical, roentgenologic, surgical and pathologic aspects.

DISCUSSION

DR. W. L. DONOHUE, Toronto Canada: Dr. Moore and his associates are to be congratulated on presenting important problems with respect to the surgical treatment of bronchiectasis. There is little doubt that Churchill, Overholt and other proponents of segmental resection in bronchiectasis have rendered a great service in bringing to our attention the anatomic segments of the various lobes of the lung and their importance in the distribution of bronchiectasis.

I think it is now time to take stock and to weigh the relative merits of segmental resection of various portions of the lung. Overenthusiasm for this particular surgical method may produce disappointing results because more complications are attendant on the segmental resection and there is also a possibility of leaving involved tissue.

It has been known for a long time that bronchiectasis occurs in the dependent portions of the lung tissue, that is, in the basal segments of the lower lobes of both lungs, the lower segment of the middle lobe of the right lung and the lingula of the upper lobe of the left lung. It is the consensus of members of both the surgical and medical staffs in the Hospital for Sick Children that, in view of the possible complicating factors, it is advisable to do a complete rather than a segmental lobectomy resection in most cases, with the following exceptions: (*a*) practically all cases in which the lower lobe of the left lung is involved, since resection of the lingula of the upper lobe of the left lung is necessary, and (*b*) cases in which there is extensive bilateral involvement, since it is necessary to preserve as much normal lung tissue as possible. As a routine in the surgical treatment of bronchiectasis I think it is the safest procedure to remove the entire involved lobe of the lung.

DR. F. W. WIGLESWORTH, Montreal, Canada: I should like merely to emphasize that this is a small number of cases and that they are of children. The majority of Churchill and Overholt's cases were of adults. We have found minimal but, to our mind, definite lesions. Nevertheless, we are not inclined to make any rigid interpretation of their evolution. They are simply present. This is the particular point I should like to leave with you, that we do not know whether these will progress. That can be determined only from extensive clinical study.

I should also like at this point to plead that bronchiectasis is an important disease and one which requires much more study, particularly in view of the more recent theory of the relation of atelectasis to bronchial ectasia and the importance of parenchymal lesions over the bronchial lesions. Perhaps, the parenchymal lesions should be emphasized rather than the bronchial ectasia.

Use of Angiocardiography and Catheterization of the Heart in Diagnosis of Congenital Cardiac Disease. DR. A. L. JOHNSON and DR. D. L. MCRAE, Montreal, Canada.

Angiocardiography in Congenital Heart Disease. DR. JOHN D. KEITH, Toronto, Canada.

Visualization of the heart and great vessels by roentgenograms taken following the injection of iodopyracet (diodrast®) intravenously provides much information to aid in the diagnosis of the anomaly present. In a study of 25 infants with this

procedure a wide variety of defects was depicted. In several infants the procedure did not add much to our knowledge of the malformation. In others the roentgenographic pictures were as positive as the results of a postmortem examination. In several infants a postmortem examination was obtained at a later date, and we were then able to compare the chambers of the heart after death with their roentgenographic appearance as visualized by iodopyracet injection. These instances form the basis of this report. The following anomalies are shown: tetralogy of Fallot, Eisenmenger's complex, tricuspid atresia, complete transposition of the great vessels, interventricular septal defect and others.

A method of taking serial roentgenograms at the rate of four per second is described and examples of its value are shown in patients with congenital heart disease, after use of iodopyracet injections.

DISCUSSION

DR. HELEN B. TAUSSIG, Baltimore: I entirely agree with Dr. Johnson and Dr. Keith that angiocardiography and catheterization are additional ways of studying malformations and that these methods help to elucidate the problems, but I feel called on to warn you that angiocardiography and cardiac catheterization are not without danger. I should like to ask both authors how much trouble they have had and whether they have lost any children during or as a result of these procedures.

We use both procedures freely in Baltimore, not in combination as Dr. Johnson does, which is a step forward if it can be safely done. One, however, cannot always be perfectly sure where the catheter is, nor can one always be perfectly sure of the relation of auricles and ventricles. In Dr. Keith's last patient was the left auricle enlarged, and was he going from the right auricle to the left auricle or from the right auricle to the left ventricle? I should like to warn you that angiocardiography may be dangerous and, if you can avoid using it, I think you should. We have had 3 deaths from angiocardiography in Baltimore. I heard of 7 deaths in California in a year and a half. That is a high mortality rate for a diagnostic procedure.

I am convinced that, in addition to sensitivity to the drug, use of angiocardiography is dangerous in any malformation in which the iodopyracet blocks the supply of oxygen to the patient. Deaths have been reported in patients with pulmonary arteriovenous aneurysms, in whom the dye was laked in the aneurysms and blocked the exchange of oxygen in the lungs. We have had 1 death from a malformation. In this patient, by the rise in the pressure on the right side of the heart, the flow of blood was blocked from left to right, thereby cutting off the supply of oxygenated blood to the patient. This possibility exists in all subjects with transposition of the great vessels because in such circumstances the aorta comes off the right ventricle, and it is the left to right shunt which directs oxygenated blood to the aorta. Therefore, we do angiocardiography with great caution in patients with complete transpositions of great vessels. A patient with cor pulmonale also died. There were pulmonary hypertension and difficulty in the oxygenation of the blood in the lungs. Consequently, although angiocardiography is a great aid, I think that the diagnosis should be made as accurately as possible first. We should consider whether it is a safe procedure for the patient before we use it universally.

DR. D. L. MCRAE, Montreal, Canada: Dr. Taussig, I am pleased to hear of your results with iodopyracet injection. We have been lucky. We have done only 60 in the past year and a half. We have not been testing the patients for sensitivity.

We have not been using the procedure in any one whose nonprotein nitrogen is over 40 mg. per hundred cubic centimeters, and to date we have had no ill effects. One patient fainted; 2 have vomited; but those are the only difficulties we have had. I am not sure, but I do not believe Dr. Keith, either, has had any difficulties. Dr. A. Castellanos, of Habana, Cuba, who, I believe, has the largest series of young children in whom angiocardiography has been performed, stated two years ago that he had never had any ill results from the procedure. As for Dr. Keith's paper, I must compliment him on the excellent quality of his slides and the rapid slide changer he has devised. It is a most valuable instrument, and we certainly ought to know more about it.

Dr. John D. Keith, Toronto, Canada: I should say to Dr. Taussig, and at the same time correct Dr. McRae's statement, that we have had 1 child die. It was a 3 year old child, and since then I have limited use of the procedure mainly to infants. I feel that if a small sensitivity test is performed the chance of running into a serious reaction are diminished. Somehow or other, the infants do seem to tolerate iodopyracet quite well in even larger amounts per unit of body weight than one would give to an older child. We started giving 35 per cent solution and we are now giving 50 per cent. I should like to give 70 per cent, and I think probably that concentration could be used with the same amount of dye. But since the concentration is greater, the bulk could be less; that is, instead of 10 cc. of 35 per cent concentration of dye, only 5 cc. of 70 per cent solution would be given, which would result in a clear outline of the defects present.

The 3 year old child who died had pulmonary atresia, and the only source of blood to the lung was a small recurrent vessel from the thyroid. The lowering of blood pressure was sufficient to cause death, but I agree with Dr. Taussig that the vast majority of conditions in the older child can be diagnosed without any recourse to catheter or angiogram. It is not necessary to put the patients through the procedure if a clear diagnosis can be made without it. In the infant, however, particularly in the newborn cyanotic infant, the angiogram adds much information.

Dr. S. Graham Ross, Montreal, Canada: May I ask on how many infants you have used angiocardiography?

Dr. John D. Keith, Toronto, Canada: I have not counted them. I think probably around 40.

Quantitative and Qualitative Blood Tests in Treatment of Congenital Syphilis by Penicillin. Dr. E. Dechene, Quebec, Canada.

Five children, from 2 to 5 years of age, bearers of latent congenital syphilis, were treated with doses of 70,000 Oxford units of penicillin G to each pound (0.5 Kg.) of body weight in order to discover the real effectiveness of the sole use of penicillin in the treatment of congenital syphilis.

Monthly tests disclosed the quantitative and qualitative modifications of the serologic reactions for the period of one year. These negative modifications were slow to appear, slower than if arsenic or bismuth had been added. However, it was a rapid progression for these patients if we consider their age and their past. One may venture to say that easier and even quicker results would have been obtained if the treatment had been given sooner and to younger children. These children have not yet been cured, but the disease has been greatly and favorably modified.

We believe a compound of penicillin and bismuth would be more beneficial.

Human Equine Encephalomyelitis in Saskatchewan. Dr. Urban J. Gareau, Regina, Saskatchewan, Canada.

Eight cases in infants of equine encephalomyelitis confirmed by the neutralization tests at the Virus Laboratory of the Rocky Mountain Laboratory (United States Public Health Service), at Hamilton, Mont., and at the Laboratory of Animal Diseases of the University of Saskatchewan, Saskatoon, Canada, have been presented; 7 recovered completely and 1 child was left mentally deficient. Because recently 2 other children have been brought in with abnormal mentality of an obscure nature, thought to be the result of encephalomyelitis in 1947, it appears advisable to check the blood of all such children against the virus of equine encephalomyelitis. A review of the history of this disease would also lead one to believe that because three epidemics of equine encephalomyelitis have appeared in southern Saskatchewan during the past ten years, members of the medical profession —at least as far as the Western Provinces are concerned—should be on guard against future epidemics.

DISCUSSION

Dr. Harry Medovy, Winnipeg, Manitoba, Canada: In the summer of 1941 and again this last summer (1947), an outbreak of western equine encephalomyelitis in infants occurred in the Winnipeg area. The cases observed presented certain problems which I think are of clinical interest and which should point the way to investigation by virus laboratories and virologists.

In the 1941 epidemic, as in the 1947 epidemic, the cases of encephalomyelitis occurred in the very young and in the very old. They were commonest in the group of infants up to about 8 months of age and in old persons. The 1941 and 1947 epidemics occurred in the middle of an outbreak of acute anterior poliomyelitis and presented many diagnostic difficulties between the two diseases. One of the interesting features of both these outbreaks was their explosive nature. In the 1941 epidemic 4 infants, all breast fed, all under 4 months of age, were in continuous convulsions in one ward at the Children's Hospital in Winnipeg. Again in 1947 3 infants were in convulsions at the same time in the observation ward at the Children's Hospital.

In 1941 the epidemic of encephalomyelitis in infants lasted about two weeks and all patients were received in the hospital within that time. One of the interesting points in the 1941 outbreak was the decided preponderance of cases of breast-fed babies. I have seen no other reference to this point. I think it is probably of some significance. Nine babies seen in the 1941 epidemic were completely breast fed; only 2 seen in the acute stage were bottle fed. The thought occurred to me, as it did to some others, that perhaps something in cow's milk protects babies against equine encephalomyelitis.

It is difficult to believe, when you see these infants in the acute stage in almost continuous convulsions for a period of two or three days, that so many of them will recover completely, yet in our series most of the babies did recover. Late sequelae developed in some of these infants. A report is in preparation on this aspect of the disease.

There is one other clinical point which I think is of some importance. In the 1941 epidemic 2 babies were seen at about 8 months of age, showing the signs of cerebral spasticity with a history of a febrile episode on the third or fourth day after birth. The histories were gone into and in both cases it was determined that this febrile episode on the third or fourth day of life occurred during the period of epidemic in Winnipeg and, concurrently, the mothers of these infants had shown a febrile disturbance. Samples of blood were drawn from the infants' mothers and

fathers, and these were tested by Dr. E. V. Casals, of the the Rockefeller Institute, New York, and at the Rocky Mountain Laboratory, by Dr. Cox, and positive complement fixation reactions for western equine encephalitis were obtained from mother and infant, with negative reactions from the father in each case. It appeared that both mother and baby had had an attack of western equine encephalitis. This favors the possibility of placental transmission of the virus. The findings are difficult to interpret, but I think the whole problem offers a fertile field for investigation by virologists.

Dr. Joseph Stokes Jr., Philadelphia: Dr. Gareau, was the distribution mostly urban or mostly rural, not only so far as incidence is concerned but also so far as the distribution of antibodies with serum collected from urban or rural areas is concerned? Was any effort made at mosquito control?

Dr. Urban J. Gareau, Regina, Saskatchewan, Canada: In early July 1947, the Saskatchewan press reported that an epidemic of equine encephalomyelitis was appearing in cattle. This report was subsequently proved to have been erroneous. Nowhere in the literature has there been any report of this disease in cattle.

In regard to the rural and urban disposition, this series was too small to draw conclusions. Three cases of the 8 reported were urban and 5 were rural. In the 1940 epidemic, the cases in Minnesota were largely rural. The cities of Winnipeg and Regina, at that time, reported cases which appeared to have had their origin within the city. This may not have meant much as these epidemics occurred in the middle of the holiday season when many persons had been at beaches and rural points. As far as mosquitos were concerned, both these cities had been infested nearly as badly as the countryside.

Dr. Medovy said in his discussion that in his series more breast-fed infants had had this disease. We have not felt this to be the case in our series.

Rh Factor. Dr. C. E. Snelling, Toronto, Canada, and Dr. W. L. Donohue, Montreal, Canada.

An attempt has been made to marshal Rh data in such a manner as to show trends and, if possible, to furnish more specific information in regard to prognosis and treatment.

In 10,916 pregnant women, 1,707 (15.6 per cent) were Rh negative and the incidence of Rh isoimmunization in the latter group was 5.4 per cent. Isoimmunization was uncommon in the first pregnancy, unless there had been a previous transfusion. Isoimmunization had its greatest incidence in the second pregnancy. If isoimmunization is present, approximately 20 per cent of pregnancies result in fetal death. The type and titer of antibodies were found to be of little prognostic value.

The infant mortality in 183 cases of erythroblastosis was 37.1 per cent. The mortality in full term infants was 29.6 per cent, and in premature liveborn infants it was 51.4 per cent. The incidence of neurologic sequelae in a group of 95 surviving erythroblastotic infants, all of whom were at least 1 year old, was 8.4 per cent.

Two cases occurred of normal Rh-positive infants being born subsequent to an erythroblastotic baby. There were 7 normal Rh-positive children born to mothers with antibodies.

Our experience with 29 replacement or exsanguination transfusions gave a mortality of 13.8 per cent. The number is small but the figures for mortality compare favorably with our previous best figure of approximately 30 per cent. In our series of 29 replacement transfusions the Coombs test was performed in

16 cases and gave a positive reaction in 15 and a negaitve reaction in 1. We feel that a positive reaction to a direct Coombs test is the most reliable early indication for a replacement transfusion.

DISCUSSION

DR. BRONSON CROTHERS, Boston: What was the experience of the authors in regard to the neurologic sequelae? It has been our experience that a reasonably large group are essentially decerebrate. No striking changes are usually seen in these children on pneumoencephalography. I have not happened to see epilepsy or hemiplegia in normal children. I should also like to know how soon after birth transfusion is performed and when it is not helpful.

DR. R. DENTON, Montreal, Canada: In view of the tremendous international interest in the Rh factor, and its implications in pregnancy and transfusion, during the past ten years, it is strange that few series of studies on cases of erythroblastosis reaching the magnitude of Dr. Snelling and Dr. Donohue's have been published. They are to be congratulated, I feel, on their thoroughness, and certainly on the good liaison between their maternity and pediatric services.

There are one or two points in which our findings in Montreal—and I think I can speak perhaps for Dr. Diamond's observations in Boston—agree with theirs. We, in Montreal, have failed entirely to find any correlation between antibody titers and antibody types and the mortality and degree of severity of the disease in newborn infants. Second, we agree entirely with the authors that prematurity is an added hazard; in fact, in our smaller series in Montreal, we have yet to find a truly premature baby, one of 5 pounds (2,268 Gm.) or less, with erythroblastosis who has survived, even though we have used replacement transfusion in many.

With respect to kernicterus, I think the frequency reported by Dr. Snelling and Dr. Donohue is perhaps a little lower than in other series, although most of the other series reported on have included not only clinical manifestations in the surviving child but also the presence of staining of basal and cerebellar ganglions in those children who died and came to autopsy.

I should like to ask Dr. Donohue one or two questions. The first concerns the state he calls "shock," leading in 1 or 2 of his cases to sudden death of the child during replacement transfusion. We have seen not only this sudden state of collapse but also, in 3 different cases, repeated attacks of tetany. These were in our earlier cases before we realized that we were administering large quantities (relative to blood volume of the recipient) of blood in which there was a considerable amount of citrate in excess of the anticoagulant needs of that blood. Therefore, this citrate could act as calcium fixer and undoubtedly was the cause of the collapse and tetanic manifestations in the infants. Since that time we have been using calcium gluconate, not only at the end of replacement transfusion but also about half through, or after each 100 cc. of replacement. The addition of this material has brought to an end the manifestations of tetany, and, with one exception, we have not had an instance of sudden collapse and death since we have been following this procedure.

Last, perhaps to continue with the suggestion proposed by Wiener in 1944 of attempting to "densitize" the isoimmune mother, and the more recent efforts of Kariher, in Rochester, with ethylenedisulfonate, to reduce the ill effects of Rh antibody on the Rh-positive and potentially erythroblastotic infant, this study brings to the fore the question that is most important of all to me in regard to Rh isoimmunization of the pregnant woman—what is the factor, or what are the factors, which protect the great majority of Rh-negative women with an Rh-positive fetus? Agreement internationally indicates that only a small proportion of those Rh-negative women bearing Rh-positive children become immunized. Why is this?

Wiener's efforts have not succeeded, and Kariher's results are as yet inconclusive. I feel that the ultimate answer in the treatment of hemolytic disease of the newborn lies in recognition and control of the factor, or those factors, which permits the immunization of a small number of mothers but protects the remainder.

DR. C. E. SNELLING, Toronto, Canada: This paper is, as Dr. Donohue said, a cooperative effort. Both he and I wish to mention here the name of Dr. Bernard Laski, assistant pathologist at the Hospital for Sick Children. Much of the material was collected by him and he did most of the serologic work.

My part in this effort has largely been in connection with the treatment of these children. The replacement transfusions, obviously, lowered our mortality. I collected figures over various stages, and at first our mortality rate was about 60 to 65 per cent. It dropped to about 50 per cent, to 45 per cent. Then, as Dr. Donohue showed, with the replacement transfusion, our over-all mortality has been 37 per cent. The mortality rate for the replacement transfusion has dropped to 13.8 per cent.

Certainly some of the failures were unavoidable, because when the child was received for treatment it probably was beyond the stage of saving. Some of the failures, I feel quite definitely from going over the records, were due to the method by which the replacement was carried out.

Dr. W. T. Mustard, one of our surgeons, has been in charge of this, but, as with any procedure that requires performance more or less immediately, often the man who is responsible is away. On the two occasions the child collapsed, Dr. Mustard was not present to supervise the procedure and it was carried out by house physicians, who, I think, did the procedure a little more rapidly than it should be done. When the times for the amounts of blood to enter and be removed were checked, they certainly were faster than he recommends.

One of the important points to remember is that blood for replacement is diluted with a certain amount of saline solution. At one time, needing a special type, we borrowed some blood from one of the other hospitals and, unknown to us, the blood was diluted to a 50 per cent solution. When we injected 100 cc. we were giving only 50. That occurred in one of the children who collapsed. I think the factor of dilution of the blood is important and should be taken into account when more blood is given at the end of a transfusion, because the child usually is already anemic.

We also give these patients a dose of penicillin at the end of the replacement transfusion by way of the umbilicus, largely because there has been a great deal of, shall I say, "mucking" about and exposure, and we feel that they need some protection. In some of the cases, especially in the one of death from peritonitis, we feel that the infection may have entered through that route.

Dr. Denton asked about the possibility of collapse from tetany; I think the citrate content is a factor we have to keep in mind. We have cut our dilution factor in the blood for transfusion with the citrate as low as possible, because we have felt it may be a reason these children were not doing well.

Mr. Chairman, I should like you to call on Dr. A. P. Hart, of the Canadian Society for the Study of Diseases of Children, to give us a short history of the first replacement transfusion with success that was done about twenty-five years ago.

DR. A. P. HART, Toronto, Canada: I feel I should tell you that I remember my old schoolmaster's statement that I was not a bad kind of boy but I lacked stick-to-itiveness, and that rather impressed me. I think if he were living today, he would say his opinion has been borne out by what has happened.

About twenty-three years ago I was called to see a baby in Toronto. It had just been born that day and I said to the father, "That is a perfectly normal, fully developed, healthy child."

He said, "Yes, this is the eighth child and they have all died except one. She was jaundiced after a few days. We carried her around on a pillow until she was a year old, and she weighed the same at 1 year of age as at birth, but she lived. The others all have died, all male children."

I saw the newborn child the next day in the evening dusk when artificial light was on and I said, "The child looks all right to me."

"No," he said, "going the way all the others have gone. I can see in the daylight that the jaundice is coming on the tip of the nose."

Well, the next day when I went there, the child was the color of a tangerine.

I had looked up the literature in the meantime, and all I could find was erythroblastosis—no, not erythroblastosis, it was not known then, but congenital icterus gravis neonatorum—with nothing at all helpful in treatment. I wondered what could be done, and, after consideration, I thought of the possibility of changing the blood. My idea was that there must be some toxin in the circulation and, of course, the father was instantly agreeable because he said, "I know it is going to go the way all the others went."

I had Dr. J. L. MacDonald do an exsanguination transfusion according to the technic of the late Dr. Bruce Robertson, who was the originator of the exsanguination transfusion, I believe. Remember, it is nearly twenty-five years ago, and I have forgotten a lot about it—he withdrew, I think, 300 cc. from the fontanel and transfused 335 cc. of blood with some saline solution into the saphenous vein.

By the next day the child was infinitely better and it continued to improve, except that in about a week it had a slight return of jaundice which we recorded as due to constipation.

This family had great confidence in me then, and, when they had another child, the ninth, they called me again. By this time an article had been published, though I do not remember whom it was published by, about using serum. I had the pathologist with me and we did everything according to this technic, but I saw that the child was rapidly getting worse. Again we gave an exsanguination transfusion. I felt it was too late; however, the child lived but kernicterus developed. It died at about 7 or 8 years of age and was extremely defective mentally.

I think you will say with my old master that I lacked stick-to-itiveness, because I did nothing more about it.

DR. VICTOR VAUGHAN, Boston: We have completed a study similar to Dr. Snelling and Dr. Donohue's, at Boston, and our results agree with theirs in every particular in regard to the expectation of recovery in liveborn babies and in the over-all group of Rh-positive fetuses of Rh-negative mothers sensitized to Rh factor.

We have had the greatest difficulty, however, in interpreting our results. It is true that the use of exsanguination transfusion at the Children's Hospital has lowered the apparent mortality of erythroblastosis fetalis to approximately the figure which Dr. Snelling and Dr. Donohue report; however, for purposes of analysis, we have divided our patients into two groups. One group is from the clinic of the Boston Lying-In Hospital, where the clientele is unselected, consisting of a relatively fixed number of Rh-negative women each year and a relatively constant number of sensitized women. There is a certain tendency for physicians to refer patients to the clinic because of previous bad results in pregnancy; however, we do not feel the tendency plays a predominant role in the formation of that group.

In that group we can find no satisfactory evidence that the mortality from this disease has changed over a fifteen year period. In the two years which were completely studied, 1946 and 1947, approximately 50 per cent of all pregnancies in Rh-negative mothers carrying Rh-positive fetuses with titer ended in the loss

of the child. Of liveborn infants 30 per cent died. These results hold for both the year preceding November 1946, in which exsanguination transfusion was not used in any child, and for the following year, in which exsanguination transfusion was used for most of the liveborn infants. The incidence of kernicterus in the two years has been the same.

At the Children's Hospital, by contrast, the number of cases seen varied widely in those years—1945, 53 cases; 1946, 30 cases, and 1947, 66 cases. The mortality also varied greatly in those years, as did the nature of the clinical material referred.

It has been our impression that factors entirely beyond our control determine the advent of kernicterus in any one of these babies. We have some families in which kernicterus has been the outcome in every Rh-positive offspring born to the sensitized mother. Included have been one family with 4 successive babies with kernicterus and another with 6 babies with kernicterus, including a set of binovular twins.

We have had the same difficulty as Dr. Snelling and Dr. Donohue in making any correlation between the type of antibody and the manifestation of disease in the child. We observed one mother who gave birth to binovular twins, one of whom was stillborn, with fetal hydrops. The placenta to which that twin belonged was large grossly and presented the usual hydropic picture on microscopic examination. The other twin was free of edema, though moderately anemic at birth. Jaundice developed soon after and it died on the second day of life of kernicterus. The placenta of this infant was normal grossly and was microscopically consistent with observed prematurity and erythroblastosis fetalis of the icterus gravis type. It seems unlikely, therefore, that the type of antibody which the mother carries determines in any way the outcome of the baby.

We have other suggestive evidence that kernicterus runs in familes and that it is genetically determined. It may prove to be simply the characteristic response to isoimmunization in certain babies.

DR. W. L. DONOHUE, Toronto, Canada: Dr. Denton raised the question of why some Rh-negative women become immunized and others do not. I do not think there is any explanation to date except perhaps the inherent capabilities of the mother for being sensitized or isoimmunized.

Poliomyelitis: A Clinical, Epidemiologic and Laboratory Study. DR. NELLES SILVERTHORNE, DR. ALICE M. GOODFELLOW and DR. CRAWFORD ANGLIN, Toronto, Canada.

Many of our patients both in the field and in the hospital were observed to have an extremely mild form of illness. These children were often well in twenty-four to seventy-two hours. The majority of our nonparalytic patients did not reveal an initial rise in total protein in the spinal fluid at the time of the first lumbar puncture, nor did an increase develop fifteen to forty-five days later. A suggestion is made from a study of two camps that the infection may have been spread through the medium of lake water used for swimming.

The study of hygienic conditions in "control" homes and in homes with poliomyelitis did not reveal significant differences, and it appeared that in most instances infection was contracted outside the home. Laboratory studies were done to determine whether other well known virus diseases of the nervous system were occurring and confusing the diagnosis of poliomyelitis. All the tests performed gave negative reactions, with the exception of one instance in which a case of mumps meningitis was discovered. Stools from 18 subjects with suspected abortive types of the disease revealed the virus of poliomyelitis in only 10.

These findings, along with the clinical observations that many of our patients had temporary illness, suggest that we may have been dealing with some other illness than poliomyelitis, or with an unusual strain of poliomyelitis virus.

DISCUSSION

Dr. A. Ashley Weech, Cincinnati: I am sorry that Dr. Albert B. Sabin, of Cincinnati, is not here to discuss this interesting paper. A study conducted by him on patients observed in Cincinnati during the late summer of 1947 has an important bearing on all investigations into the epidemiologic aspects of poliomyelitis. During the summer season approximately 170 cases of recognizable poliomyelitis occurred in metropolitan Cincinnati. Concurrent with these diagnosable cases were an estimated 10,000 or more cases of summer sore throat or summer influenza. These patients with summer sore throat did not show the signs of meningeal irritation which commonly lead to a suspicion of preparalytic or nonparalytic poliomyelitis. Nevertheless, 13 of them were hospitalized to permit testing the hypothesis that the large epidemic might be due to infection with the virus of poliomyelitis. The results of the study validated the hypothesis. Among 10 patients whose signs and symptoms were compatible with what was being diagnosed as summer sore throat or influenza, poliomyelitis virus was demonstrated in material from the pharynx and stools in 5 and in another antibodies for the Lansing virus appeared during convalescence; in still another patient in this group, pleocytosis was demonstrated, despite the continued absence of nuchal or spinal rigidity. It is noteworthy that 4 of the 5 strains of virus obtained from these patients were of especially low virulence for monkeys, in contradistinction to the higher virulence of strains recovered simultaneously from patients with the paralytic disease.

If the experience in Cincinnati is corroborated by studies in other localities, it would seem that the problem of the epidemiologic characteristics of poliomyelitis was much larger than that following the spread of paralytic and recognizable nonparalytic poliomyelitis. Even more important will become an understanding of those conditioning factors which determine the development of a crippling disease in 1 child in perhaps 50 or more infected with the virus.

Dr. Samuel Karelitz, New York: I should like to comment on the spinal fluid changes in the convalescent stage to which Dr. Silverthorne referred. While I was in the Army, I had the experience of trying to make a differential diagnosis between Guillain-Barré syndrome and poliomyelitis in a soldier who was in the eighth week of his illness. His spinal fluid protein was 260 mg. per hundred cubic centimeters. His progress was typical of that in poliomyelitis. This led to a study at the Willard Parker Hospital, in New York, two years ago. In more than 100 children admitted to the hospital with poliomyelitis, the spinal fluid protein was determined on their admission and then prior to their discharge from the hospital, or in three to six weeks. I cannot give you the figures exactly at this moment, but in 25 per cent or more of those with paralysis there was an appreciable rise in the protein content from, in some patients, 40 or more mg. to as high as 130 to 160 mg.

A fascinating case illustrating this point is published in the *New York State Journal of Medicine*, in which there was a mounting protein, I think up to 1 per cent, or 1,000 mg. This increase continued for several months until the patient's death. The postmortem observations were typical of poliomyelitis.

Incidentally, I might mention that I had a similar experience in a patient with wound diphtheria with paralysis in whom the spinal fluid protein was high. I followed this patient for a few months, during which time the spinal fluid protein remained at about 150 mg. Because of this observation I examined the spinal fluid

of 8 patients with acute faucial diphtheria. In 1 of them the serum protein was elevated to 65 mg. In 12 patients with postdiphtheritic paralysis most of the spinal fluids revealed high protein levels, ranging from 55 to about 150 mg.

Although these observations were new to me while I was overseas, they are by no means original. I think they are interesting in view of Dr. Silverthorne's observations and in view of the fact that more and more observers are finding these same changes.

Dr. Harold K. Faber, San Francisco: I am greatly interested in Dr. Weech's statements about summer sore throat. Sore throat has been one of the common early symptoms of poliomyelitis in our experience, occurring in about 10 per cent of cases and, I notice, in 11 per cent of Dr. Silverthorne's. We have seen it in a fairly high percentage of our cases to be a precursor of bulbar poliomyelitis.

Some of you may be interested in the theory we have proposed, that the virus most commonly enters through the pharyngeal mucosa, probably through the peripheral nerves of the fifth, ninth and tenth cranial nerves, first infecting the ganglions and then going on into the central nervous system.

I have had the feeling that sore throat is closely related to this process and that in some of the abortive nonparalytic cases the infection may be almost entirely limited to these peripheral ganglions. That may possibly be the case in the Cincinnati epidemic of sore throat. I cannot prove this at the moment, but it is anatomically reasonable.

Dr. Nelles Silverthorne, Toronto, Canada: I am glad to have these suggestions of Dr. Weech in respect to the symptom of sore throat. I did not want to take time to mention that many of our hospital patients had sore throat, as well as headache, fever and vomiting. Some of the children in our field studies had these same symptoms in places where cases of paralytic poliomyelitis were occurring, but some of them did not have meningeal signs or increased numbers of cells in their spinal fluid.

Dr. Weech mentioned the oral pharynx. This year we wondered whether the reason we were not obtaining virus in the stools of some of our children with nonparalytic attacks was that the virus was in the oral pharynx at the time they were examined. We expect to do more this year on pharyngeal washings. Some of the monkeys showed a form of paralysis, and it is difficult to explain this observation in the absence of poliomyelitis lesions in the cords of the monkeys given injections of material from the stools of those with nonparalytic attacks.

Dr. Karelitz, we also observed a large number of paralytic patients, 39 per cent, as I mentioned on the slide, who had increased total protein in the cerebrospinal fluid, but, in addition, we had 61 per cent who, eleven to forty-five days after onset, did not reveal rises in the total protein of the cerebrospinal fluid, and these were definitely paralyzed children.

Some Observations on the Children of Hiroshima and Nagasaki, Japan. Dr. William W. Greulich, Stanford, Calif.

Causation of Ekiri, a Highly Fatal Disease of Japanese Children: I. Clinical and Bacteriologic Studies. Dr. Katharine Dodd, Cincinnati, and Dr. C. John Buddingh, Nashville, Tenn.

Ekiri is a highly fatal disease of Japanese children in the age group of 2 to 6 years which is prevalent in the summer season. It is characterized chiefly by convulsions, high fever, diarrhea and vomiting. The course of the disease is short, with death occurring within four to forty-eight hours of onset. The disease had

heretofore been studied only by Japanese workers who disagreed widely concerning its causation.

Although the incidence of bacillary dysentery is extremely high in Japan and dysentery bacilli could be cultured in about half of the children with ekiri, its clinical picture appeared at variance with that of dysentery.

A study carried out in the summer of 1947 under the auspices of the Japanese National Institute of Health and the Public Health and Welfare Section of the Supreme Command of the Allied Forces showed that in the clinical picture symptoms of tetany were in the foreground. Rigidity of the musculature with stiffness of the face and carpopedal spasms, twitchings and convulsions and involvement of the autonomous nervous system were among the most frequent signs. The triad of high fever, hyperventilation and convulsions dominated the disease picture in the patients who died. Conditions diagnosed as dysentery in patients of the same age group also included tetanic manifestations which appeared to differ only in degree from those of ekiri. The effects of calcium therapy were often dramatic and appeared to support the assumption of the importance of tetany.

The bacteriologic studies yielded dysentery bacilli in 90 per cent of the patients studied. In more than 40 per cent Shigella sonnei was the pathogen, in 30 per cent the Flexner strain and in 30 per cent Shigella ambigua. Postmortem examinations showed the dysentery to be mild in the majority of the patients. Edema of the brain was the main pathologic observation.

II. Chemical and Nutritional Aspects. Dr. Samuel Rapoport, M.D., Cincinnati.

The chemical disturbance in patients with ekiri was characterized by low serum levels of calcium, a decrease in carbon dioxide content and tension of the blood and high levels of nonprotein nitrogen. The low calcium levels appeared compatible with the clinical signs of tetany. The decreased carbon dioxide tension and the presence of normal p_H values were evidence of the extreme degree of hyperventilation that was observed clinically. The elevation of the nonprotein nitrogen appeared explicable by the great losses of water caused by high fever and hyperventilation, added to losses of body fluid through vomitus and diarrhea.

An inquiry into possible nutritional causes of the tendency to hypocalcemia yielded the information that the Japanese diet is low in calcium, the daily intake of adults being less than 0.3 Gm., and high in phosphorus, so that the calcium to phosphorus ratio is 1:7. The average milk consumption is extremely low, about 1.2 cc. per day per member for the city population. Japanese infants are breast fed for the most part and are weaned at 1 to 2 years of age. The diet of children does not differ in composition from that of adults, so that the calcium consumption of children 2 to 6 years of age is about 0.15 Gm. per day. Rickets is uncommon.

An orienting study was carried out by 29 Japanese children 2 to 6 years of age. Mild signs of tetany were observed in a considerable proportion of the children; 5 showed serum calcium levels below 9 mg. per hundred cubic centimeters. The phosphorus levels of the whole group tended to be higher than those of control American children. The serum alkaline phosphatase was considerably elevated, with 12 of the children showing values in excess of 10 Bodansky units. Roentgenographic examinations of the bones gave no evidence of rickets but suggested decreased mineralization.

DISCUSSION

Dr. A. Ashley Weech, Cincinnati: We have heard the story of grim death and mutilation at Hiroshima and Nagasaki. We have listened to the record of a mission of mercy sent by a governmental agency to discover the cause of a

disease which has been killing large numbers of Japanese children. The debt owed to those who in innocence suffered can fittingly be paid only by missions which return to the people enhanced health and happiness.

The tens of thousands killed or maimed by the atom bombs is indeed greater than the number who die in any one year from ekiri. Nevertheless, the annual mortality from ekiri is numbered in the thousands. The thought might well be in our minds that it is only a question of time, and the length of time depends on how swiftly the new knowledge can be disseminated, before more lives will have been saved because of the mission than were lost through the atom bombs.

Symposium on Virus Diseases

Organization and Functions of a Virus Diagnostic Laboratory. Dr. Joseph Stokes Jr., Dr. Michael Sigel and Dr. Werner Henle, Philadelphia.

Basic studies on viruses and rickettsias have made possible the diagnosis of several diseases caused by these agents through the development of special procedures, as well as the adaptation of known serologic methods.

The Virus Diagnostic Research Laboratory at the Children's Hospital of Philadelphia was organized as a division of the Virus Research Laboratories. This position enables the laboratory to apply new procedures to its diagnostic work as they evolve in the research laboratories and to channel specimens of special interest to the individual research laboratories.

The function of the laboratory consists of three phases: (1) diagnostic work on specimens from individual cases, (2) studies on outbreaks and epidemics and, (3) research.

By the use of serologic procedures, such as the complement fixation, agglutination, hemagglutination-inhibition and neutralization tests, the laboratory can aid in the diagnosis of a number of viral and rickettsial diseases. Between October 1946 and April 1948, this laboratory rendered confirmatory or differential diagnoses of cases of influenza, ornithosis, atypical pneumonia, mumps, in particular mumps meningoencephalitis, lymphocytic choriomeningitis, herpes simplex and Rocky Mountain spotted fever.

Information concerning the causation of epidemics can often be obtained. In many outbreaks, the origin must be determined by isolation of the virus in susceptible animals or chick embryos. This procedure is usually supplemented by serologic tests. Occasionally, in outbreaks of a disease with a characteristic clinical picture, serologic tests may be sufficient. This laboratory has collaborated in epidemiologic studies on outbreaks of influenza, mumps and poliomyelitis.

Research problems are continually being presented along the lines of both improvement of diagnostic methods and unusual developments in clinical and epidemiologic patterns.

Infections with the Virus of Herpes Simplex. Dr. T. F. McNair Scott, Dr. Lewis L. Coriell and Dr. Harvey Blank, Philadelphia.

Only in recent years has the disease-producing potentiality of herpes simplex virus been recognized. The concepts of primary infection, latent infection and recurrent manifestations have further clarified the role of this virus in human disease. A brief summary of the clinical manifestations of herpes simplex is presented with special emphasis on acute herpetic gingivostomatitis, which is by far the commonest clinical manifestation of primary infection.

Serologic studies with the neutralization tests carried out in embryonated eggs are presented to show the behavior of neutralizing antibodies in primary and in recurrent infections, as well as in apparent infections. The incidence of acute herpetic gingivostomatitis in a group of clinic patients is correlated with presence of antibody in the group.

Encephalitis: Isolation and Identification of Virus from Body Fluids in Human Subjects. Dr. Russell J. Blattner and Dr. Florence M. Heyes, Houston, Texas.

In a study of a series of patients with signs and symptoms of central nervous system involvement, attempts were made to show the presence of virus in peripheral blood and in spinal fluid. All these patients showed pleocytosis in the spinal fluid; however, any with positive bacteriologic cultures or with findings diagnostic of tuberculous meningitis were eliminated from the series.

From 1943 through 1947, 81 patients with encephalitis were studied for the presence of virus in the peripheral blood. Blood taken from the patient was heparinized and promptly inoculated in white Swiss mice or on the chorioallantoic membrane of the fertile egg. A virus was isolated from 1 of these patients. A 9 year old boy was seen in July 1945 with signs and symptoms suggesting encephalitis. From his blood stream the virus of St. Louis (type C) encephalitis was isolated. During clinical recovery this patient displayed increasing antibody titer to the newly isolated virus and to a known strain (Hubbard) of the virus of St. Louis encephalitis. Simultaneous inoculation of spinal fluid failed to reveal the presence of virus.

From 1940 to 1947, 304 spinal fluids were inoculated on the chorioallantoic membrane of the fertile egg and in white Swiss mice. Distribution of the cases by years is as follows:

	No. of Cases		No. of Cases
1940	14	1944	55
1941	23	1945	60
1942	41	1946	42
1943	57	1947	7

Virus was isolated in 7 patients; 5 strains of lymphocytic choriomeningitis virus, 1 strain of vaccinia virus and 1 strain of herpes simplex virus were found.

In the last patient, herpes simplex was isolated also from brain tissue taken at autopsy and pathologic studies of the brain revealed that the virus had entered the central nervous system through the olfactory nerve. All the pathologic changes noted in the brain were present in the olfactory portion.

Mouse protection tests were done on the serums of 152 patients; 17 of these showed increasing antibody titer to the virus of St. Louis encephalitis.

In summary, the virus of St. Louis encephalitis was isolated from the peripheral blood stream in 1 of 81 patients, or 1.2 per cent. Five strains of lymphocytic choriomeningitis, 1 strain of vaccinia virus and 1 strain of herpes simplex were isolated from spinal fluid in 7 of 304 attempts, or slightly over 2 per cent. Of 152 patients, 17 showed increasing antibody titer to St. Louis encephalitis virus, or approximately 11.0 per cent.

DISCUSSION

Dr. Joseph Stokes Jr., Philadelphia: Since I have had a minimal amount to do with the studies reported and the development of the diagnostic laboratory, as described by Dr. Sigel, perhaps I can speak somewhat more objectively con-

cerning the value of virus diagnostic laboratories, particularly from the public health aspect, entirely aside from the interesting observations reported by Dr. Blattner, Dr. Coriell and Dr. Sigel on individual cases.

I should like to mention the laboratory's significance from the public health standpoint as far as influenza epidemics, mumps and Q fever are concerned. Some years ago when my associates and I reported before this society early results on vaccination against influenza virus, type A, two points were outlined that have remained strikingly clear throughout succeeding years in the study of epidemic influenza. One was the possibility of immunizing solidly against influenza virus, and the other was the appearance, in general, in the blood stream of a certain critical level of antibodies which could be used as an approximate dividing line between susceptibility and resistance in groups of persons studied.

These two tools have been of increasing significance in public health because they have made possible the utilization of vaccines against a specific virus in protection of large groups of the population. The study of the levels of immune bodies also made possible determinations of the density of susceptible persons in various groups of the population throughout the world. With the isolation of influenza virus type B by Francis and Magill, together with new strains of influenza virus type A, it has been possible to add these viruses to the vaccines.

By means of virus diagnostic laboratories, we are able, as Dr. Sigel mentioned, to have listening posts or watching posts throughout the world for the isolation of viruses, such as antigenically new strains of influenza viruses, types A or B, which can be added, if necessary, to the basic vaccines obtained in preceding epidemics. There is considerable evidence that in the major epidemics of influenza, types A and B, small groups of cases or epidemics occur either during the spring or during the summer in other countries or in outlying areas, as, for instance, the Hawaiian Islands and Puerto Rico. The pandemic of 1918 may have spread from abroad to this country. It is entirely possible that the addition of such virus strains to the vaccine would be of great assistance in the protection of various populations.

I do not believe that the study of the density of susceptible persons by means of serums is nearly as important a question as the isolation of the virus, but results of such studies may be used as a tool for epidemiologic investigations in diagnostic laboratories.

As far as mumps is concerned, it is of interest, as Dr. Sigel pointed out, that in a fair percentage of patients the encephalitis is caused by mumps virus, without any accompanying parotitis.

Dr. G. John Enders and Dr. Fred R. Hobbins, of Boston, told me their experience during the past winter was similar. They had many patients with mumps encephalitis without parotitis. Thus, a fair percentage of the cases of encephalitis throughout the country must be caused by the mumps virus. Dr. Sigel has shown you the results from Toronto, which Dr. Silverthorne mentioned in his report, and the results from Sweden. Thus, a virus diagnostic laboratory in one area can study epidemics in outlying areas.

Q fever is spreading throughout the country and requires for its diagnosis the type of facilities we have been discussing. It has been epidemic in Southern California and in Texas. The virus is present in milk, in cattle and in goats in large quantities in specific areas. Apparently, the disease is not contracted by ingestion but by inhalation. This means that meatpackers and persons working in dairies where there is dust, or wherever inhalation of the organism may occur, are at risk. It is a dangerous organism with which to work in the laboratory.

as indicated by the past experience of many workers, but samples of blood obtained during the acute and succeeding convalescent stages will permit diagnosis.

If the virus diagnostic laboratory uncovers an epidemic, a therapeutic trial of aureomycin or chloramphenicol (chloromycetin®) could be arranged for control of the disease.

The question then remains, of course, of the way in which such virus diagnostic laboratories should be set up. It has appeared to us that the plan is workable only when such laboratories supply large areas of the country, possibly covering two to four states. It is not feasible, apparently, for each medical school to turn over its virus laboratory for such studies, because a virus laboratory studying specific infections and carrying forward a considerable research program is not so equipped that its personnel can go out at a moment's notice to investigate epidemics. It appears better to have areas supplied by virus diagnostic laboratories in the manner of those of the State Department of Health at Berkeley, Calif., the Army Medical School and the Department of Health in New York city. Such laboratories have a real purpose not only for the prevention but also for the detection of epidemic disease.

DR. T. F. MCNAIR SCOTT, Philadelphia: I should like to comment on one or two points regarding the herpes problem. In the first list of diseases caused by the herpes virus, recurrent stomatitis was entered with a question mark. At the moment I think the recurrent solitary aphthous ulcers can be taken out of that list. We have found no evidence that such recurrent solitary aphthous ulcers are due to herpes. We have studied them intensively and obtained the virus from none of them. The biopsy specimens have shown no characteristic histologic features, and in 2 patients with such recurrent ulcers neutralizing antibodies for herpes were absent from the blood. The more extensive recurrent stomatitis is, I think, still a subject for further investigation. Some of the cases are probably due to herpes, but probably only a small proportion of them.

I was much interested in Dr. Blattner's patient who died of herpes meningoencephalitis. The case raises the question of the way persons are infected with herpes. Herpes obviously must be an ever present virus, and yet some epidemiologic considerations, as pointed out by Burnet particularly and by Andrews, indicate that the incidence of the disease is different at various socioeconomic levels. Now, if the herpes virus is airborne like that of the common cold, it seems almost inconceivable that a difference in incidence according to socioeconomic level should be as pronounced as it apparently is. Many fewer patients in the higher socioeconomic levels have neutralizing antibodies than in the lower.

Some factor, such as close contact, may have to be present before infection takes place. The greater crowding of persons in the lower socioeconomic levels might favor this. In some of the patients with acute herpetic gingivostomatitis there is a history of trauma. We recently saw an adult who had trauma of the gums, with development of typical acute primary herpetic stomatitis. In this patient of Dr. Blattner's I wonder how the olfactory nerve was infected. One perhaps might postulate actual trauma to the nose, such as irritative crusting, with picking of the nose, as a mode of entrance for the virus.

One more point—I think, the difference in the concept of the primary infection, which demands for its manifestation exposure to the herpes virus, from that of the recurrent manifestation of herpes, which does not demand exposure to the virus, needs emphasis. The recurrent manifestations, as far as I can make out, are entirely unrelated to contact and are initiated by some nonspecific trigger mechanism.

This concept, I think, leads us to the fundamental problem of the reason certain persons have clinical manifestations of herpes. As Dr. Coriell and others have pointed out, there is a happy relationship between the host and the herpes parasite. When this happy relationship is marred in some way, the patient gets sick, and we want to know why. This is similar to the question raised earlier of why certain patients get symptoms of paralysis from poliomyelitis and others do not; why some patients who have had a herpetic infection never, or hardly ever, show a recurrent manifestation of herpes, while others have them every month, or every two or three months.

I think we have to turn our attention to the question of the basic physiologic characteristics of the cells and the intimate relationship of the virus and the host cell.

Dr. Lewis K. Sweet, Washington, D. C.: I should like to ask Dr. Blattner and Dr. Sigel if they have any information on the distribution of the virus in the spinal fluids of various cell counts. We have been reviewing recently 20 patients with lymphocytic choriomeningitis, in whom the diagnosis was proved by Dr. Charles Armstrong and his associates at the National Institutes of Health, Bethesda, Md., either by recovery of the virus from the spinal fluid or by demonstration of a definite increase in antibody titer in the blood. The point that interests me is that the cell counts in these spinal fluids ranged from about 150 to over 3,000. In those patients in whom the spinal fluid cell count was above 1,000, we routinely recovered virus. Among those in whom the spinal fluid cell count was under 1,000, we recovered the virus from 1 or 2, and the disease in the remainder was diagnosed by demonstrating a rise in antibody titer.

I should like to know whether the virus is free in the spinal fluid or is attached to or contained in the cells. If the latter were true, we might centrifuge the spinal fluid, use the cellular sediment for animal inoculation and thus recover the virus more frequently. We have sent out hundreds of spinal fluids to get 20 cases of choriomeningitis diagnosed.

Dr. Russell J. Blattner, Houston, Texas: I have no information on that particular point; however I believe that virus may be present in body fluid in quantities insufficient to produce clinical signs of encephalitis in mice, even when the body fluid is injected intracerebrally in the mice. On the other hand, inoculation of such materials on the chorioallantoic membrane of developing hen's egg may allow multiplication of the virus present to a titer sufficient to be demonstrated by mouse inoculation.

In our work with St. Louis encephalitis, with the use of chickens, viremia was readily demonstrated by the fertile egg passage technics but on no occasion were we able to show the existence of viremia by inoculation of heparinized blood directly from the chick embryo into mice. I think that the sensitivity of the method used for the detection of virus is extremely important. In our experience there was no obvious correlation between the spinal fluid cell count and success in demonstrating of virus.

Dr. M. Michael Sigel, Philadelphia: The question of isolation of virus from the spinal fluid in reference to the cell count may perhaps be related to the time the specimen is taken. Assuming that a high cell count corresponds to the early acute stage of illness, one is more likely to isolate the virus from a fluid showing many cells, whereas spinal fluid taken several days after onset, when the cell count has begun to decline, may be expected to contain less virus.

The second point I should like to make is that in our experiences frequently a suspected case of lymphocytic choriomeningitis is diagnosed in the laboratory

as mumps meningoencephalitis. I think it has been shown that mumps meningoencephalitis exceeds in frequency lymphocytic choriomeningitis on the order of, maybe, 5 or 10 to 1.

In regard to isolation of a virus in chick embryos and mice, I believe that in a virus diagnostic laboratory, where one is concerned primarily with a diagnosis by any means whatsoever, one can perhaps rely on the simplest and most economical means, in this case serologic tests. It is not necessary to prove the presence of the virus in the spinal fluid or blood in order to make such a diagnosis. It is only when antigens are not available or when one is dealing with a new entity that one should try isolation of a viral agent.

Active Immunity in Tetanus. Dr. J. J. Miller Jr., Dr. M. L. Ryan and R. R. Beard, San Francisco.

A review of the 30 reported cases of tetanus occurring in actively immunized personnel of the British and American armies permit the following conclusions: Immunization with toxoid is remarkably effective. Rare fatal cases of tetanus, however, may occur after incubation periods as short as two days. Thorough primary immunization and routine reinjections will minimize such failures. In cases of severe wounds with shock, the prophylactic administration of antitoxin, as practiced by the British, may lower the case fatality rate.

The speed of mobilization of antitoxin in response to reinjections of tetanus toxoid was studied in a group of more than 150 actively immunized children and adults. A striking variation in speed of response during the subsequent week was observed. Apart from individual differences in the capacity of the immune mechanism, the speed may depend on (1) the adequacy of the primary immunization, precipitated toxoid being preferred to fluid toxoid; (2) the type of toxoid used for reinjection, fluid toxoid being preferred, and (3) the interval between the primary immunization and the reinjection. When this interval is greater than four years, the response may be slowed.

Experimental evidence is advanced indicating that, although the presence of circulating heterologous antitoxin interferes with primary immunization, it does not prevent the secondary (anamnestic) response to a reinjection of tetanus toxoid. It is, therefore, suggested that the maximum prophylactic effect against tetanus in severely wounded immunized persons (and/or when immunization occurred more than four years previously) may be obtained by simultaneous injection of toxoid and antitoxin in different extremities.

DISCUSSION

Dr. Amos U. Christie, Nashville, Tenn.: For the past three years at Vanderbilt University, Nashville, Tenn., Dr. J. C. Peterson and I have been attempting to study this and related problems. We set up an investigation which is designed to test first the ability of young infants, as well as older persons, to respond to multiple antigens. The basic study consists of the use of 80,000,000,000 organisms in phase I pertussis vaccine, 60 to 65 Lf units of diphtheria toxoid, 200 to 220 minimum lethal dose equivalents of tetanus toxoid, all adsorbed on aluminum hydroxide. These are given to healthy infants 4 weeks of age or older in a series of three injections six weeks apart to arrive at the totals I have indicated. Specimens of blood taken initially, at six week intervals and, after the first six months, at three month intervals are checked for antitoxic and agglutinin titers.

I should like to show you the results of some of these studies which are pertinent to Dr. Miller's paper.

[Slide] This is a result of the responses to tetanus antitoxin; in these infants the pattern of antibody response to the multiple antigen for tetanus antitoxin is excellent. The levels for all the infants are well above 0.1 unit, the usually accepted protective level.

[Slide] This second slide shows the same material broken down by age. I think it is apparent that quantitatively there is no difference. Very young infants respond as well as older persons.

[Slide] However, the pattern of response with diphtheria toxoid is different. About 15 to 25 per cent are relatively poor immunizers. Passive immunity from the mothers seems to neutralize or inhibit the production of active immunity. I should like to call your attention also to the fact that even among the babies studied for diphtheria antitoxin there were relatively poor immunizers. In other words, in this group of infants who have some passive immunity, there is a neutralizing effect to the initiation of primary immunity, at least as produced by multiple antigens. In the data on immunity to pertussis shown in the second slide, somewhat the same effect is revealed.

[Slide] This section of the slide represents those infants who had a titer of less than 1 to 50. In the next section are those infants who had a titer of 1 to 50 or more of agglutinins before pertussis immunization. In the latter the pattern is seen to be considerably different. The infants with evidence of passive transfer pertussis antibody did not acquire protective levels of agglutinins nearly as frequently as those without passive transfer antibody.

The clinical implications are several. Perhaps it makes one a little hesitant to attempt to immunize very young infants. Perhaps the neutralizing effect of passive immunity plays some part in those who show relatively poor response to diphtheria toxoid and to pertussis vaccine. None of the mothers had immunity or none of the babies had passive immunity for tetanus antitoxin, so the infants' response was entirely different and much better.

Dr. John A. Bigler, Highland Park, Ill.: I think Dr. Miller has brought up several interesting questions concerning what should be done with the person who has received basic immunity with tetanus toxoid. What is the length of time basic immunity can be depended on; can one depend on the toxoid booster, and, third, should one also give tetanus antitoxin with the toxoid booster? The figures from the Army indicate that a good basic immunity can be established. There were only about 8 cases of tetanus reported in the United States forces, in which nearly 10,000,000 men were immunized and several hundred thousand suffered wounds or injuries. Of these 8 patients, 3 had not received a booster injection.

It seems possible to me that in these few persons the failure to develop immunity may have occurred. We do know that not all persons will react the same way to tetanus toxoid. We also know that all persons do not react the same way to tetanus antitoxin. We titrated antitoxin levels after the administration of tetanus antitoxin and found some children had practically none in the blood stream on the second day, though the average child would have a sufficiently high level for seven days.

The other question that comes up is whether or not the fluid toxoid has any advantage over the alum-precipitated toxoid. We have found that in the establishment of basic immunity the alum-precipitated toxoid is, as Dr. Miller observed, more effective than the fluid toxoid. We have given several children injections with boosters some years after their basic immunity, and our results with the alum-precipitated toxoid as a boostering agent were about the same as those Dr. Miller showed with the fluid tetanus toxoid.

I should like to show a slide of information on one of the children for whom titration was performed. We do daily titrations on several after the administration of the booster dose.

[Slide] In 1939, this 1 year old infant was given her first dose of 1 cc. of diphtheria and tetanus toxoids, alum-precipitated. Three months later the child received a second dose of 1 cc., and at this time the antitoxin titration showed more than 0.003, but under 0.001 unit. One month later she had between 2 and 5 units of antitoxin. Then titrations were made in 1944, in 1945, in 1946, and again in 1947, with levels of more than 0.001 but less than 0.1 unit.

A booster dose of 0.5 cc. of alum-precipated tetanus toxoid was given in 1947 and that day the antitoxin level was 0.017 unit. Twenty-four and forty-eight hours later it remained the same, but on the third day it went up to 0.05 unit and remained the same on the fourth day. On the fifth day she had 0.1 unit; on the sixth day 0.5 unit, which is as high as we have ever observed with administration of 1,500 units of antitoxin. On the sixth day the level was up to 1, and thirteen days after the administration of the tetanus toxoid booster she had 4 units. We know from other studies that this level continues to rise for a period of four to six weeks, at which time it reaches a peak and then begins to decrease.

I show this slide to amplify the figures Dr. Miller has given. The alum-precipitated toxoid in our experience has been as effective as the fluid toxoid. I am not convinced at present that it is necessary to give tetanus antitoxin at the time of injury, because of the almost negligible number of cases reported in the armed services after immunization and booster injections.

The figures from the British Army are somewhat different in that tetanus toxoid boosters were not used, and for a long period tetanus toxoid was given on a voluntary basis. In a group that received no tetanus toxoid, there was a fairly high incidence of tetanus. In a second group that received fluid tetanus toxoid without a booster, but with tetanus antitoxin, the incidence of the disease was reduced dramatically. Yet according to the figures from the American forces, in which a booster dose is used, the incidence was much further reduced, possibly within the realm of error.

Follow-up Study of Patients Who Have Recovered From Meningitis.

Dr. John A. V. Davies, Dr. Edith Meyer and Dr. Harriet Hyde, Boston.

This study concerns 105 children who recovered from different types of meningitis in the years 1940 to 1947. Physical and psychologic examinations were given within three months to eight years after discharge from the hospital. The group includes 17 with pneumococcic meningitis, 34 with meningococcic meningitis and 54 with Hemophilus influenzae meningitis. Of those with H. influenzae meningitis, 30 were treated with streptomycin and 24 with sulfadiazine and serum. The development of these children who were under 2 years of age at the onset of their illnesses was in general considerably poorer than those 2 years of age or over. In the younger children who had recovered from meningitis, good results were observed in 8 per cent of the pneumococcic group; in 28.6 per cent of the meningococcic group; in 33.3 per cent of the H. influenzae group treated with serum and sulfonamides, and in 48.2 per cent of the H. influenzae group treated with streptomycin. In the older children, good results were seen in 40 per cent of the pneumococcic group; 42 per cent of the meningococcic group; 59.9 per cent of the H. influenzae group treated with sulfonamides and serum, and 66.6 per cent of the H. Influenzae group treated with streptomycin.

Evidence of brain damage varied from severe motor and mental damage in the younger group with pneumococcic meningitis and severe mental damage in the younger group with meningococcic meningitis to behavior disturbances in the younger group with H. influenzae meningitis who received serum and sulfadiazine. The patients with H. influenzae meningitis treated with streptomycin show, so far, a small incidence of behavior disturbances. The result in the older children was a small incidence of impairment in those with meningococcic meningitis and in those with H. influenzae meningitis treated with streptomycin. No impairment was found in the children with pneumococcic meningitis and in those with H. influenzae meningitis treated with sulfadiazine.

The patients followed up were an unselected group. The distribution according to age groups was uneven.

DISCUSSION

Dr. Stuart S. Stevenson, Boston: I was especially interested in the group of children whose intelligence quotients were within a reasonably average range of normal and who did not have obvious neurologic defects but who showed personality and behavior difficulties.

Neither Dr. Davis nor Dr. Meyer mentioned the fact that these children were not evaluated within the first three months after recovery from the acute phase of their illness. Most of them were evaluated after six months, I believe, which would seem to avoid the proximate sequelae of the acute illness. I think these children represent a group which in times past might have been neglected as normal. Presumably, as Dr. Meyer pointed out, more damaged children are surviving now than previously because of better treatment, and the problem of these children is one of increasing magnitude as treatment improves each year.

I think it is unfortunate that the personality traits of these children before their acute illness could not always be ascertained, but I do not think Dr. Meyer and Dr. Davies have to apologize for any unavoidable incompleteness in their data. This is a most important group of cases for study. It represents one more class of children whose psychiatric difficulties seem to have anatomic bases. As Dr. Davies said, they suggest that we must evaluate the therapy of meningitis with a longer perspective for future effects and that we must not evaluate merely in terms of mortailty and gross neurologic sequelae. We are learning to treat such children as we do those with rheumatic heart disease, teaching them to live with their crippling conditions and to adapt to them. I think many of these children who need psychiatric aid must be helped in terms of the concept of an anatomic defect which we may not be able to cure but for which we may be able to prescribe ways of life that will help them cope with their incurable disabilities.

Dr. Hattie E. Alexander, New York: Such standards as those described by Dr. Davies and Dr. Meyer for evaluation of patients who recover from meningitis should be the aim of all of us. Most of us have fallen far short of them. However the gross evaluation of the mental and physical status in the studies of my colleagues and me has provided some interesting data. Of the 72 recovered patients, or 80 per cent of the total of 90 patients treated with sulfonamides and specific rabbit antiserum, there were no children who showed gross mental or physical defects. In the group of about 45 who were treated with streptomycin alone or, when necessary, with other adjuncts, 86 per cent recovered but 4 of these were grossly defective children.

Our experience suggests that the degree of cerebral injury present at the time of treatment determines the outcome with either of the two froms of therapy. The patients in whom the cerebritis is irreversible reveal clinical signs of encephalitis early. The patient continues to have a high fever and to be in a comatose state even when the spinal fluid shows improvement; signs of involvement of the motor cortex are characteristic. The use of all three agents, sulfonamides, antiserum and streptomycin, has permitted the survival of 4 of these patients who probably would have died from the infection if treated with only antiserum and sulfonamides. We have not yet been able to demonstrate a significant difference in the results of treatment between the combined action of sulfonamides and rabbit antiserum and that of streptomycin in conjunction with sulfonamides. It is important to emphasize that sulfonamides play an important role, namely, the elimination of organisms which are resistant to streptomycin.

Dr. Honor Smith, Oxford, England: I have been intensely interested by this paper of Dr. Davies and Dr. Meyer, and I also find it disquieting, because now that recovery from the commoner types of purulent meningitis can be expected it is imperative that we should know how often and how far this recovery is worth having.

In a series of 50 consecutive patients with pneumococcic meningitis treated at Oxford, 11 patients were 2 years of age or younger. All these patients received penicillin intrathecally, often by the ventricular route, and many, in addition, received penicillin and sulfadiazine systemically. Of this group of 11 infants, in 8 my associates and I considered the final results satisfactory. These children have now been followed for two to four years, and their degree of recovery has been gaged from the absence of fits, from the absence of neurologic signs, from their behavior at home and from their capacity to hold their own with their contemporaries.

Of the remaining 3 patients, 2 were moribund when admitted to the hospital and died a few hours later; the third had had active, uncontrolled or partially controlled meningitis for over five weeks and had already acquired a severe "posterior basic" syndrome when she came to us for treatment. She, unfortunately, survived and has remained a severe mental and physical cripple.

From these experiences, and from comparable patients in the older age groups, we have come to consider early institution of treatment as the most important prognostic factor. Indeed, we consider a case of pneumococcic meningitis as among the most acute of all medical emergencies.

Of the 8 patients who made a satisfactory recovery, many were critically ill during the acute phase of their illness. Fits were a menace and relapse a commonplace; yet, in spite of their immediate danger to life, these factors did not seem to influence the ultimate outcome.

I should, therefore, like to ask Dr. Davies and Dr. Meyer whether they have found any correlation between the stage of the illness when chemotherapy, or rather when effective chemotherapy, was first begun and the incidence of the disabling sequelae, and also at what stage of the illness they feel that it may be possible to predict the ultimate outcome.

Dr. Edith Meyer, Boston: I will answer only the last part of Dr. Smith's question and I do not know how well I can answer it. I think we have found that those children who on discharge from the hospital are still unresponsive and have severe motor disability are likely to keep on having difficulties. We have had, however, a few children discharged with slight motor involvement which cleared up within the first two or three months. I think it is fair to say that if after three months the difficulty is still present it is likely to persist.

I should add this: We have followed more carefully those children treated with streptomycin than any others. We try to see them on discharge, four weeks, three months, six months and a year from discharge, so that we should, as time goes on, get a fairly good picture of the course of recovery.

Origin and Nature of Resistance to Streptomycin of Gram-Negative Bacilli. DR. HATTIE E. ALEXANDER and DR. GRACE LEIDY, New York.

Experimental data suggest that large populations of all species of bacteria possess a similar defense mechanism against any clinically effective antibacterial agent. The members that defend the race through their capacity to thrive in concentrations of the agent which are injurious to the masses are present before exposure to the antibiotic. They breed true; therefore, as a result of their reproduction and elimination of the sensitive members the strain emerges resistant.

There is now ample evidence that this principle holds for resistance of Escherichia coli to specific bacteriophage, of E. coli to ultraviolet and roentgen rays, of staphylococci to penicillin, of Streptococcus pyogenes to penicillin, of staphylococci to sulfathiazole and of Hemophilus influenzae to streptomycin.

The present report offers proof that six other gram-negative bacilli, Hemophilus pertussis, Hemophilus parapertussis, E. coli, Eberthella typhosa, Salmonella newport and Pseudomonas aeruginosa, are also equipped with a comparable mechanism. Highly resistant variants have been demonstrated in large populations of all these species; they occur spontaneously as the result of bacterial mutations. The rate of occurrence of these mutants has been studied in relation to their bearing on the therapeutic importance of emergence of resistance in an organism to a given antibiotic.

The therapeutic implications are discussed.

DISCUSSION

DR. JOSEPH STOKES JR., Philadelphia: Dr. Alexander, do subcultures become sensitive and does biologic passage through animals make the resistant organisms sensitive?

DR. HATTIE E. ALEXANDER, New York: Our experimental results demonstrate that resistance to 1,000 micrograms per cubic centimeter is an inherited trait in each one of the gram-negative bacilli studied; after ten to twenty subcultures in streptomycin-free medium it was not possible to demonstrate a significant change in the degree of resistance. However, in each species a fraction of the colonies which grew in pour plates containing 1,000 micrograms of streptomycin per cubic centimeter behaved differently. The results suggest that two mutations are responsible for their behavior, resistance to streptomycin and a change in nutritional requirements; they grew well in the presence of streptomycin but poorly or not at all in absence of this antibiotic. The details of our experience with these members of Hemophilus influenzae have already been reported.

Chemotherapeutic Studies of Tumors, Including Leukemia, in Children. DR. SIDNEY FARBER, Boston.

The justification for chemotherapy in children with malignant tumors is the assumption that further therapeutic attempts are warranted in situations where the technics of surgical treatment and radiation are of no value. Recent research

has demonstrated the possibilities for a combination of chemotherapy with established forms of treatment of malignant tumors. A brief summary is made of the temporary benefits obtained with the use of nitrogen mustards (*tris*[β-chloroethyl]amine hydrochloride and methyl-*bis*[β-chloroethyl]amine hydrochloride) and of observations on the action of folic acid conjugates and antagonists on malignant tumors of infants and children.

The acceleration of the leukemic process produced by folic acid conjugates and experimental studies concerning folic acid deficiency in the rat led me to the suggestion that folic acid antagonists might be of value in the treatment of patients with acute leukemia, with or without pretreatment with folic acid or folic acid conjugates. The possibility of more effective action of irradiation therapy or nitrogen mustards after pretreatment with folic acid or folic acid conjugates was also suggested.

Studies have been made on four series of children treated with folic acid antagonists, which were supplied or synthesized by Dr. Y. Subbarow and his colleagues of the Lederle Laboratories, Pearl River, N. Y., and the Calco Chemical Co., Inc., Bound Brook, N. J. Studies on 14 children with acute leukemia carried out with the collaboration of Dr. Gilbert Lenz, Dr. James W. Hawkins, Dr. Robert E. Mercer and Dr. E. Converse Pierce, concerning the action of a folic acid antagonist, pteroylaspartic acid, and on 7 children treated with methylpteroic acid showed that these agents were responsible for slow and moderate changes in the bone marrow and hematologic picture, and that the course of the acute leukemia was definitely prolonged in a few instances.

The action of the most powerful agent so far employed, 4-aminopteroylglutamic acid ("aminopterin") and of another antagnoist, 4-amino-10-N-methylpteroylglutamic acid ("amethopterin") was studied by a group which included Dr. Louis K. Diamond, Dr. Robert Mercer, Dr. Robert Sylvester and Dr. James A. Wolff. Observations were made on 28 infants and children who were treated for periods varying from twenty-one to one hundred and sixty days. Approximately 70 per cent showed improvement clinically, hematologically and in the bone marrow to a degree and of a character not encountered in previous experience. Comparison of the observations in these patients with the clinical and hematologic findings collected in more than 300 children with acute leukemia by Dr. Louis K. Diamond, and with our own pathologic studies comprising more than 200 postmortem examinations on infants and children with acute leukemia, permits the conclusion that the changes observed in children treated with folic acid antagonists, particularly "aminopterin," may be attributed to the use of the substances employed. The remissions produced by the use of "aminopterin" are of temporary nature and include a restoration approaching normal in the hematologic picture, including thrombocyte levels, disappearance of immature cells from the peripheral blood and the bone marrow and reduction in the size of the liver, spleen and lymph nodes.

"Aminopterin" is a toxic substance and may be responsible for severe stomatitis, for aplasia of the bone marrow and for other toxic effects which are described. Studies with these agents indicate that a promising direction for further research concerning the nature and treatment of acute leukemia in children has been found. The use of chemotherapeutic agents now available and the readiness to employ those which are certain to be described from many sources in the next few years should do much to reduce the number of instances of "incurable cancer" in infants and children.

Congenital Anomalies of Heart and Great Vessels in Offspring of Vitamin A-Deficient Rats. Dr. James G. Wilson, Rochester, N. Y., and Dr. Josef Warkany, Cincinnati.

Congenital malformations affecting the eyes and genitourinary tract of fetal and newborn rats from mothers maintained in severe vitamin A deficiency during pregnancy have already been described. The heart and major arteries in 43 such defective offspring have also been studied by means of microscopic serial sections and wax-plate reconstructions. In 17 of these fetuses the cardiovascular system was abnormal. Anomalies of the embryonic aortic arches were observed in 13 fetuses. Right-sided aortic arch, in which the right rather than the left fourth embryonic arch was retained, was found in 4 instances. Double aortic arch, in which both fourth embryonic arches remained to encircle the trachea and esophagus, was noted in 2 animals. In 5 fetuses both fourth arches were absent and the connection between the heart and the descending aorta was effected through the ductus arteriosus alone in 2 animals and through one or both persisting third embryonic arches in 3 animals. In 2 of the latter group of 3 animals there was an extreme degree of pulmonary stenosis, associated with interventricular septal defect and enlarged ascending aortic trunk. Other arterial anomalies, such as absence of common carotid, subclavian arteries running posterior to the esophagus and subclavian arteries arising from the ductus arteriosus, were also present in several of the aforementioned fetuses. In 2 additional animals the only arterial anomalies were a right subclavian artery that arose from the descending aorta and coursed behind the esophagus and a right subclavian artery that arose from the right pulmonary artery.

A defect in the interventricular septum was associated with these arterial anomalies in 9 animals. In 4 fetuses which had a normal arterial pattern a defect of the interventricular septum was the only anomaly found. Although relatively small numbers of fetuses and newborn animals have been studied, there is strong indication that fewer animals survive to, or near, full term with defects of aortic arches than with interventricular septal defects. Varying degrees of deficient myocardial development have been observed throughout this series of offspring from vitamin A-deficient mothers.

DISCUSSION

Dr. Helen B. Taussig, Baltimore: It must have been tedious and time consuming to work out the pattern of all the arches. I should like to ask whether these anomalies were associated with anomalies of the spine, because in human beings I have been impressed by the number of congenital malformations of the spine associated with malformations of the aortic arches in combination with malformations of the heart causing persistent cyanosis. Have you any idea why we see anomalies of the aortic arch, particularly the aortic ring, in noncyanotic malformations, while the right aortic arch occurs so frequently in the cyanotic group? We have seen only 2 or 3 instances of an aortic ring in cyanotic persons, whereas 20 per cent of all the cyanotic patients with tetralogy of Fallot have a right aortic arch.

Dr. James G. Wilson, Rochester, N. Y.: Regarding associated abnormalities in the central nervous system, particularly in the spine, I can say only that of the specimens we have studied to date no central nervous system defects have been identified. As to Dr. Taussig's second question, I feel that I am not qualified to comment on the subject.

Three New Syndromes Causing Persistent Cyanosis Which Are Compatible with Life for a Number of Years. Dr. Helen B. Taussig, Baltimore.

The first of these is a new malformation. It is a complete transposition of the aorta combined with a large overriding pulmonary artery which arises from the right ventricle, partially overrides the ventricular septum and receives blood from both ventricles. Clinically, this malformation resembles the Eisenmenger complex in many features. The malformation is compatible with life for a number of years. The child does not squat. The heart is slightly, if at all, enlarged; on fluoroscopy there are fulness of the pulmonary conus and pulsations in the hilar shadows. The electrocardiogram shows right axis deviation and right ventricular hypertrophy. This malformation differs from the Eisenmenger complex in that cyanosis dates from birth and exercise shows a fall in the oxygen consumption per liter of ventilation.

The second malformation is that of complete transposition of the great vessels combined with an enormously dilated pulmonary artery. The aorta arises from the right ventricle and the dilated pulmonary artery arises from the left ventricle and may or may not slightly override the ventricular septum. The clinical manifestations of this malformation are similar to those of other cases of complete transposition of the great vessels except that the malformation seldom leads to progressive cardiac enlargement. Therefore, the condition may be compatible with life for a number of years. The child squats when tired. The roentgenographic and fluoroscopic findings are distinctive. The heart is slightly enlarged; there is a concave curve at the base of the heart to the left of the sternum, and exaggerated vascular markings extend far out into the pulmonary fields. On fluoroscopy there are conspicuous hilar pulsations.

The third clinical syndrome is comparatively rare. It is a complete transposition of the great vessels with a pulmonary artery of normal size; the additional anomalies are such that the malformation does not lead to rapid progressive cardiac enlargement. The condition may be compatible with life for a number of years. In childhood the contour of the heart closely resembles that in the tetralogy of Fallot. Indeed, it differs from a tetralogy of Fallot mainly in the quality of the vascular markings. These are denser than those cast by the minute vessels of extensive collateral circulation; furthermore, the vascular markings extend far out toward the periphery of the lungs. The hilar markings show many small dense circular shadows due to blood vessels which are viewed on end. These vascular markings are difficult to see on fluoroscopy. The discrepancy between the vascular markings appearing in the roentgenograms and those visible on fluoroscopy is of diagnostic significance. Physiologic studies are of no aid in the differentiation of a complete transposition of the great vessels from a tetralogy of Fallot. Angiocardiography may or may not be of aid and may be dangerous.

Correct diagnosis of these malformations is important, as none of these are amenable to correction by a Blalock-Taussig operation.

DISCUSSION

Dr. John D. Keith, Toronto Canada: This is an angiogram I thought you might be interested in seeing. It is of a 5 month old child who was cyanotic from birth but not severely so. A moderate systolic murmur and a moderately enlarged heart with considerable pulsation in the hilar region were noted. This angiogram was taken one and a half second after the beginning of the injection of

the iodopyracet; the right auricle and ventricle are filled, and the aorta has filled immediately from the right ventricle. It appears that the aorta is coming off mainly from the right ventricle, perhaps entirely so. The pulmonary artery is taking dye readily from the right ventricle and appears a little larger than the aorta. Apparently, it also is coming off the left ventricle as suggested both by its shape and by the fact that there is a little thickening of the shadow in this area of the pulmonary artery. I suggest this is probably a case that would fit in with Dr. Taussig's group 101.

Certainly her cases are extremely interesting and I think we should be grateful to her for pointing out the clinical signs that will help us to identify them.

DR. F. W. WIGLESWORTH, Montreal, Canada: Speaking in one sense, the first two syndromes of Dr. Taussig are, I think, not entirely new. The Eisenmenger complex I understand from the late Dr. Maude Abbott consisted of an overriding aorta or an aorta rising from the right ventricle. We have had 3 cases in the last four years; 1 patient was 17 years old, with the aorta arising entirely from the right ventricle and questionable septal overriding of the pulmonary artery, as Dr. Taussig has illustrated.

In the second group, the transposition with the enormous pulmonary artery, I recently had a case of a 10 year old child who had an enormous pulmonary artery, and I wondered whether Dr. Taussig encountered in her case evidence of arteriosclerosis. We found difficulty in trying to differentiate the stem of the pulmonary artery from the two branches, because of the extreme dilatation. The right branch was so large that we mistook it, to begin with, for the aorta. It showed severe atherosclerosis.

I should like to ask Dr. Taussig about the Eisenmenger complex, whether she includes the added classification whereby the aorta could be completely arising from the right ventricle. We have had several cases and I know Dr. Abbott in her "Atlas of Congenital Cardiac Disease" (page 44) stated that the aorta may be dextroposed or completely over in that group.

The third syndrome I am not acquainted with, but we have had several cases of the other two.

DR. PHILLIP E. ROTHMAN, Los Angeles: Dr. Taussig has, I think, given the impression that a correct diagnosis in the atypical cyanotic malformations is often possible clinically without the necessity for catheterization of the heart, determination of circulation time and angiocardiograms. In the typical tetralogies I think it is generally believed that a correct diagnosis can be made in more than 90 per cent of the cases without any of the elaborate tests. However, it is already apparent that the number of typical cases of tetralogy is diminishing and that my associates and I are seeing an increasing number of atypical cases in which it is extremely difficult to make a diagnosis in order to determine whether surgical intervention is justifiable.

I have the impression that elaborate methods of diagnosis are necessary in more than 40 to 50 per cent of these cases. If that is true, then in hospitals and pediatric services that do not have completely equipped cardiac departments two possibilities arise: One is that all persons with atypical malformations are to be sent to completely equipped cardiac centers, and the other that exploratory operations be done and the decision based on a direct determination of the pressure in the pulmonary artery.

In the beginning of our work, when we had more difficulty in diagnosing the typical tetralogies, operation was inadvertently performed in some of the cases that were not tetralogies. After a direct determination of the pressure in the pulmonary artery, when it was seen that the cases were not suitable for surgical treatment,

the wound was closed without any danger to the patient. I wonder whether Dr. Taussig believes that we would arrive at a correct determination in the majority of cases by an exploratory operation.

DR. HELEN B. TAUSSIG, Baltimore: I had understood from the original description of an Eisenmenger complex that the aorta arose from the left ventricle and partially overrode the right ventricle, and that Eisenmenger did not consider an aorta arising entirely from the right ventricle with a ventricular defect beneath the pulmonary artery as the same malformation or as a variant of it.

I have been criticized by Dr. Arnold Rich for considering a malformation as an Eisenmenger complex when the pulmonary artery was not abnormally dilated, but I believed that the malformation was comparable to the auricular defects and the Lutembacher syndrome, namely, that with congenital or acquired mitral stenosis and an auricular septal defect, the pulmonary artery may be of normal size or it may be abnormally large. We have seen some malformations of the Eisenmenger type without a greatly dilated pulmonary artery and a few in which the pulmonary artery was abnormally large.

As regards the question concerning complete transpositions of the great vessels with an enormously dilated pulmonary artery, I think this combination of anomalies is frequently compatible with life for a number of years. We have seen several children in the older age group in whom the pulmonary artery was so enormously dilated that the main branches of the pulmonary artery were the size of the aorta. I have not, however, had an opportunity to examine such conditions at autopsy; hence, I have no indication how early arteriosclerotic changes appear.

In answer to the question concerning diagnosis by exploratory operation: I suppose at times all are confronted with it, and certainly we have made our mistakes in diagnosis, as well as other persons have. The one great difficulty is that at operation one sees a relatively small area. Dr. E. A. Park used to ask me whether the diagnosis was right, and I would say we saw a little of the right auricle and the superior vena cava, and one subclavian artery and the pulmonary artery, but we had no idea of the internal structure of the heart. The surgeon can measure pulmonary pressure; in the complete transpositions of the great vessels pulmonary pressure is usually high. However, the pressure probably depends on the direction of the shunt. Dr. Alfred Blalock has operated on 2 patients by mistake in whom the pulmonary pressure did not seem to be abnormally high. Therefore, in the last analysis, exploratory operation is not usually helpful and diagnosis should, whenever possible, be made prior to operation.

Originally, Dr. Blalock took 250 mm. of water as the maximum pulmonary pressure. It is only fair to say that we were selecting patients with extreme pulmonary stenosis and the lowest pressures. Then he took 300 mm. of water. Recently, he has operated on a number of patients with a pulmonary pressure of 400 mm. of water, and he has reoperated on a few patients on whom he previously would not operate because of high pressure. Four hundred millimeters of water is about the normal pulmonary pressure. It is true that in some of the patients with a patent ductus arteriosus pulmonary pressure may be abnormally high, and the flow of blood is still from the aorta to the pulmonary artery. Therefore, operation may be proved to be indicated with a higher pulmonary pressure than 400 mm. of water. Indeed, last week, Dr. Blalock operated on one patient with a pressure of 500 mm. of water, and the child has done well.

In the last analysis, the question is how the patient does over a period of months and years. If the diagnosis is wrong, the result is disastrous. If the child is cured or greatly improved by operation, it indicates that the child suffered from inadequate pulmonary blood flow.

Diagnosis of Hyperinsulinism. Dr. Edward M. Bridge and Dr. David H. Weintraub, Buffalo.

Difficulties are frequently encountered in distinguishing hyperinsulinism from other forms of hypoglycemia. Five cases of hyperinsulinism have been studied and the data compared with those on normal animals that received excessive doses of insulin. The results led to a clearer understanding of the physiologic actions of insulin and offered a basis for the diagnosis of human hyperinsulinism.

The observations which have proved of most value in distinguishing hyperinsulinism from other forms of hypoglycemia are the following: (*a*) the intensity of the hypoglycemic tendency, (*b*) the rate of fall in blood sugar following a normal meal, (*c*) the changes in the respiratory quotient during the development of hypoglycemia, (*d*) the absence of ketosis at the time of hypoglycemia and (*e*) the muscle glycogen level.

These criteria are consistent with the known physiologic effects of insulin. The hypoglycemia of hyperinsulinism is a result of the excessive rate of deposition of muscle glycogen. The liver is unable to put out glucose at a correspondingly increased rate and deficiency in the blood results. Other forms of hypoglycemia might be called hepatic in origin, for in them a faultily functioning liver is unable to put out sufficient glucose to meet the needs of simple starvation.

Book Reviews

Technique of Treatment for the Cerebral Palsy Child. By Paula F. Egel, Cerebral Palsy Director, Children's Hospital, Buffalo. Introduction by Winthrop M. Phelps, M.D., Medical Director, Children's Rehabilitation Institute, Baltimore. Appendix by Moir P. Tanner, F.A.C.H.A., Superintendent, Children's Hospital, Buffalo. Drawings by Dorothea Mintline. Price, $3.50. Pp. 203, with 49 figures. The C. V. Mosby Co., 3523-25 Pine Blvd., St. Louis, 1948.

This book gives the author's views on the management of cerebral palsy as obviously interpreted from the point of view of Dr. Winthrop Phelps, a recognized authority in the field.

The first four chapters deal with the medical aspects of the problem and the remaining chapters pertain to the actual technics employed. The book would be improved if the chapters relating to the history, classification, differential diagnosis and psychiatric aspects of the problems therein were omitted. They are a veritable storehouse of misinformation and would have best remained unwritten.

The other chapters give a worth while description of the technics employed by Dr. Phelps and the author. Even here, however, there are certain sections, like those on relaxation and on confused motion, which must be considered as somewhat ambiguous, sketchy and, to say the least, controversial.

One of the best chapters is the final one, in the form of an appendix, based on the organization of a cerebral palsy department in a children's hospital, which was prepared by Moir P. Tanner, superintendent of the Children's Hospital in Buffalo.

In spite of its many misstatements, the book can be recommended for technicians treating children with cerebral palsy. It would be of no great value to parents, since its medical portions are so unauthentic and its technical portions are beyond their comprehension. A glaring omission is the absence of a chapter on parental training. The books adds nothing original to the subject and is simply a repetition of previously published material.

The book is printed on good paper, is well bound and contains adequate illustrations.

Nursery School Guide: Theory and Practice for Teachers and Parents. By Rhoda Kellogg, Supervisor, Golden Gate Nursery Schools, San Francisco. Price, $4. Pp. 501, with 44 illustrations. Houghton Mifflin Company, 2 Park St., Boston, 1949.

For any one contemplating the establishment of a nursery school, this book will be an invaluable guide. It is a source of accurate information for a physician who is seeking to understand the aims, principles and problems involved in the operation of a nursery school. It is particularly useful to professional teachers

and students. For the parent who wishes to know more in detail of what is done in nursery schools, it will be exceedingly helpful.

It is not a book on just the theory of nursery education but is a guidebook of specific information regarding the practical procedures and technics used in well regulated nursery schools. It describes in detail the buildings, equipment, materials, program, teaching technics and methods of discipline employed in nursery schools. It tells how the schools are organized, what records are kept, what kind of relations are established with the parents, what the requirements for staff members are, all in terms of a program oriented to the needs of a public school system.

This book differs from others dealing with nursery schools in that it is written by an expert in the field who had firsthand experience with the private nursery school and later great familiarity with the public nursery school. Any significant extension of nursery schools must be geared to the public school system. A teacher-pupil ratio must be maintained that is consistent with broad educational policies and yet can supply good nursery education. The author's descriptions of nursery school operation are based on a departure from the technics and methods described in books based on a ratio of 1 teacher to 4 or 6 children. The schools referred to maintain a 1 to 10 teacher-pupil ratio and obviously supply excellent nursery education.

Every phase of nursery school operation is thoroughly discussed, but not in so much detail that one becomes confused. To each chapter is added a list of selected reading material that enriches the value of the book.

The chapters on health, nutrition, emotional disturbances and health practices are well prepared. The information would be helpful to a physician if he were at all interested in the health of school children.

The appendixes are devoted to specific outlines that cover every phase of a nursery school. With the numerous excellent photographs portraying many of the daily activities, the book represents a complete and sound exposition of the nursery school that is today recognized to be an essential part of the program for child education.

Cardiac Catheterization in Congenital Heart Disease: A Clinical and Physiological Study in Infants and Children. By André Cournand, M.D.; Janet S. Baldwin, M.D., and Aaron Himmelstein, M.D. Price, $4. Pp. 108, with 159 illustrations. The Commonwealth Fund, Division of Publications, 41 E. 57th St., New York, 1944.

The authors present in this monograph a concise exposition of the methods employed and the knowledge to be gained by cardiac catheterization in infants and children.

The first part of the book is divided into four chapters. The first chapter deals with the equipment, technics and procedures which are used, together with the precautions to be observed in avoiding undue risk to the patient.

The second chapter illustrates the various positions of the catheter in the heart and great vessels as seen under the fluoroscope.

The third chapter shows the characteristic pattern of the blood pressure tracings, while the final chapter sets out the formulas for the calculation of systemic and pulmonary blood flow and of blood shunts.

In the second part of the book the authors present 17 case histories illustrating the various types of anomalies frequently encountered in the noncyanotic group. The clinical data, together with cardiac signs and roentgenologic findings, are coordinated with the physiologic studies and a final evaluation is made from the information thus obtained.

This book is well written, authoritative and timely. The ever-increasing success of surgical treatment in the field of congenital cardiovascular anomalies demands that every practical available means be utilized in the effort to arrive at an accurate diagnosis. Cardiac catheterization is one of these means.

There has been much misconception concerning the supposed ease and simplicity of this procedure. The authors make it clear that the technics are exacting and that a well trained and coordinated team is necessary to secure satisfactory data and to insure the safety of the patient. To the physician who is interested in this highly specialized field, this book can be wholeheartedly recommended.

Post-Traumatic Epilepsy. By Arthur Earl Walker, M.D. (American Lecture Series No. 20). Price, $2.75. Pp. 86, with 20 illustrations and 6 tables. Charles C Thomas, Publisher, 220 E. Monroe St., Springfield, Ill., 1948.

This clearly printed and well bound little volume gives an excellent summary of the known facts about post-traumatic epilepsy. The author, who is widely known in his field, is now professor of neurologic surgery at the Johns Hopkins University, Baltimore, and has had considerable experience with the patients about whom he writes. He discusses, briefly of course, the incidence, pathogenesis and physiologic aspects of epileptic attacks due to trauma and describes the type of attack. There are a brief chapter on medical treatment and, as might be expected, a longer one on surgical treatment. The latter is precisely clear and easily understood. A bibliography and index complete the volume. This book should be a handy reference work for the general practitioner, the pediatrician and the neurologist.

Enuresis or Bedwetting. By R. J. Batty, M.D. Second edition. Price, 9s. 6d. Pp. 103, with 9 figures and illustrations. New York: Staples Press, Inc., 1948.

This little book, written by an experienced English clinician, is said to be the only monograph in the English language dealing with enuresis. It contains much that is excellent in relation to the organic factors involved in the condition, though small importance is placed on the etiologic and therapeutic factors of its emotional aspects.

It may be that enuresis in England stems from causes unlike those in America. The author's statements that "oxyuriasis is present in more than 31 per cent of my cases," that "I have made it a rule to begin treatment of all enuretics with an anthelmintic" and that "one-third of those who had tonsillectomy and adenoidectomy were cured of their bedwetting immediately" reflect a point of view at variance with that of American observers.

There is a long bibliography of more than 95 references, of which only 5 are to articles published since 1940. Those especially interested in the subject will find this book of value as a work of reference. Those seeking practical help for the solution of this often baffling clinical problem might be more misled than benefited by the book.

Your Child or Mine: The Story of the Cerebral-Palsied Child. By Mary Louise Hart Burton, in collaboration with Sage Holter Jennings. Price, $1.25. Pp. 64, with 11 illustrations. Coward-McCann, Inc., 2 W. 45th St., New York, 1949.

This booklet consists of short case reports of 6 children with cerebral palsy. The case histories are more or less realistic, illustrative of some of the problems which are encountered with these children and written in simple language. The booklet is primarily intended for parents and laymen interested in knowing what a child with cerebral palsy looks and acts like.

There is an attached bibliography of fair quality, and a rather inadequate list be recommended as interesting reading for parents of children with cerebral palsy.

The book is well printed and illustrated with excellent photographs. It can be recommended as interesting reading for parents of children with cerebral palsy.

Diabetes and Its Treatment. By Joseph H. Barach, M.D., F.A.C.P. Price, $10. Pp. 326, with 73 figures, 60 tables and 317 diet charts. Oxford University Press, 114 5th Ave., New York, 1949.

This first volume is another good textbook on diabetes mellitus. The author, who has had wide experience in this field of medicine, has written a most interesting history of diabetes.

The chapters on the treatment of juvenile diabetes and the diabetes of pregnancy are well written but brief.

The final section of the book is devoted to diets for diabetic persons of all ages. This section may be considered superfluous by some; to others, who treat occasional patients with diabetes, it may be most valuable.

Formula para determinar la racion alimentaria del recien nacido prematuro. By Horacio L. Burgos. Price, none given. Pp. 48, with 22 tables. El Ateneo, Florida 340-Córdoba 2099, Buenos Aires, Argentina, 1948.

This interesting little monograph written in Spanish is based on the author's studies on the nutrition of premature and full term newborn infants. He concludes that to attain correct growth one must fulfil the laws of nutrition. To obtain these ideal results, he has devised the following formula:

$$\frac{A\,(DL-1)}{N\,O\,D} = Ad.\,All$$

in which A means allowance in grams, $DL-1$, days of life less one, $N\,O\,D$, number of days needed to reach the definitive allowance and $Ad.\,All$, the adaption allowance in grams. Many examples are given of the adaption of this formula to actual instances. His patients all appear to have gained weight satisfactorily. Although written in Spanish, the book is easily read by anyone interested in this problem.

Stuttering. By Charles Van Riper. Edited by Wendell Johnson. Prepared for the American Speech and Hearing Association. Free of charge. Pp. 60, with 9 illustrations. The National Society for Crippled Children and Adults, Inc., 11 S. La Salle St., Chicago, 1948.

This booklet reviews the modern concepts of stuttering generally agreed on by authorities in the field of speech disorders. The pamphlet is intended for the nonprofessional public but has much value for professional persons as well. Stuttering is described in both children and adults. The usual onset of stuttering in young childhood, the problem of examination and location of this onset and the general methods of treatment by parents and others are covered from the point of view of the general public. Suggestions for parents which have been proved helpful by a number of clinics are given and the general method of correction used by professionally qualified speech correctionists is outlined.

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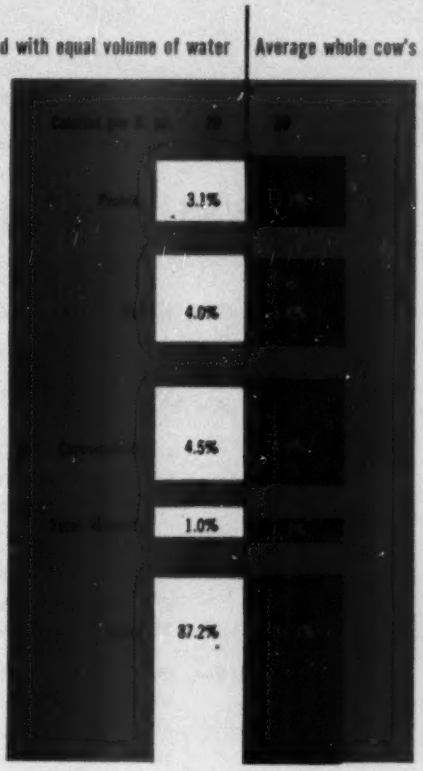

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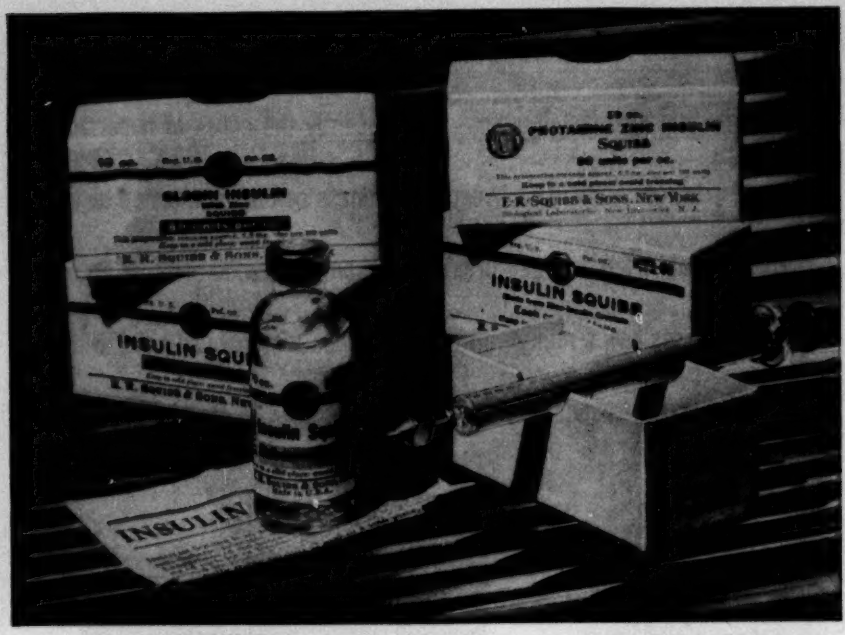

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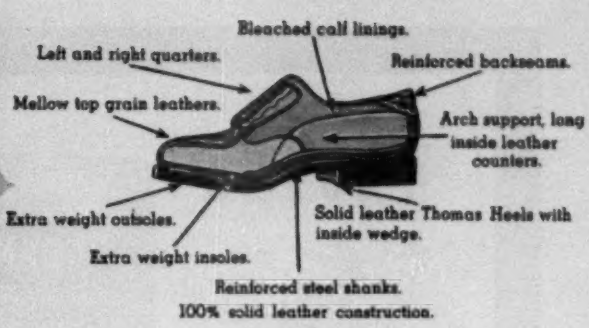

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